NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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   b. Leukaemia Care
   c. Lymphoma Action
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Document B

Company evidence submission

October 2019

File name	Version	Contains confidential information	Date
NICE VenG for CLL Document B	Final	Yes	29th October 2019

Contents

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Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criteria
ALC	Absolute lymphocyte count
ASO-PCR	Allele-specific oligonucleotide polymerase chain reaction
Bcl2	B-cell lymphoma 2
BCRi	B-cell-antigen receptor inhibitor
BCRP	Breast cancer resistant protein
BIC	Bayesian information criteria
BNF	British National Formulary
BR	Bendamustine with rituximab
BSA	Body surface area
BSH	British Society for Haematology
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIRS	Cumulative illness rating scale
CLL	Chronic lymphocytic leukaemia
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CrCl	Creatinine clearance
CRi	Complete response with incomplete bone marrow recovery
CRR	Complete response rate
CSR	Clinical study report
CYP3A	Cytochrome P450-3A
DSU	Decision Support Unit
ECOG	European Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End-of-treatment
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ERG	Evidence Review Group
FCR	Fludarabine, cyclophosphamide and rituximab
FISH	Fluorescent in-situ hybridisation
FUM	Follow-up month
GClb	Chlorambucil with obinutuzumab
G-CSF	Granulocyte-colony stimulating factor
HCHS	Hospital and Community Health Services

Abbreviation	Definition
HDMP	High-dose methylprednisolone
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality-of-life
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
iDMC	Independent Data Monitoring Committee
IGHV	Immunoglobulin heavy-chain variable region
IPD	Individual patient data
IPI	International Prognostic Index
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat population
IV	Intravenous
IVRS	Interactive voice response system
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LY	Life years
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MDASI	MD Anderson Symptom Inventory
MMRM	Mixed-effects model repeated measures
MRD	Minimal residual disease
NCI-CTCAE	National Cancer Institute common terminology criteria for adverse events
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service
NMA	Network meta-analysis
NMB	Net monetary benefit
OATP	Organic-anion-transporting polypeptide
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PO	Oral
PPS	Post-progression survival
PR	Partial response

Abbreviation	Definition
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
Q2W	Once every two weeks
QALY	Quality-adjusted life year
QD	Once daily
RClb	Chlorambucil with rituximab
RCT	Randomised controlled trial
R/R	Relapsed or refractory
SAE	Serious adverse event
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TLS	Tumour lysis syndrome
ToT	Time-on-treatment
TSD	Technical support document
TTNT	Time-to-next treatment
Tx	Treatment
VAS	Visual analogue scale
VenG	Venetoclax with obinutuzumab
VenR	Venetoclax with rituximab
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The European Medicines Agency (EMA) marketing authorisation for venetoclax in combination with obinutuzumab (VenG) is expected in [redacted], with the anticipated license wording being: Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

This submission focusses on a narrower scope in relation to the anticipated marketing authorisation for VenG. The submission will concentrate on VenG in the two subpopulations listed in Table 1.

Table 1: Sub-populations considered in this submission

Population	Comparison	Rationale
Subpopulation 1: Patients with previously untreated CLL, without del(17p)/*TP53* mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR	VenG vs GClb	• This subpopulation best reflects the cohort of the pivotal trial, CLL14 • The subpopulation is consistent with NHS clinical practice; clinical experts treating patients with CLL in the UK NHS have confirmed that VenG would not be used in patients suitable for fludarabine- or bendamustine-based therapies
Subpopulation 2: Patients with previously untreated CLL, with del(17p)/*TP53* mutation	VenG vs ibrutinib monotherapy	• This subpopulation is also reflected in the pivotal trial, CLL14, where 10.6% of patients has del(17p)/*TP53* mutation • There is a high unmet need for this poor-prognostic subpopulation

Abbreviations: CLL: chronic lymphocytic leukaemia; GClb: chlorambucil with obinutuzumab; NHS: National Health Service; VenG: venetoclax with obinutuzumab.

These two distinct populations and corresponding relevant comparators are addressed by the decision problem for this submission, as summarised in Table 2.

The company submission presented here is consistent with the final NICE scope and the NICE reference case.

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated chronic lymphocytic leukaemia	People with untreated chronic lymphocytic leukaemia with coexisting conditions that make fludarabine and bendamustine based therapy unsuitable for them	The CLL14 trial population does not include patients who would receive FCR or BR in clinical practice, as advised by UK NHS clinicians
Intervention	Venetoclax with obinutuzumab	As per final scope	As per final scope
Comparator(s)	Without a del(17p)/*TP53* mutation: • Fludarabine, cyclophosphamide and rituximab (FCR) • Bendamustine with or without rituximab (BR), for people for whom fludarabine-based therapy is unsuitable • Chlorambucil with or without rituximab, for people for whom fludarabine-based therapy is unsuitable • Obinutuzumab with chlorambucil, for people for whom fludarabine-based therapy and bendamustine is unsuitable With a del(17p)/*TP53* mutation: • Ibrutinib alone, for people for whom chemo-immunotherapy is unsuitable • Idelalisib with rituximab	Without a del(17p)/*TP53* mutation: • Obinutuzumab with chlorambucil With a del(17p)/*TP53* mutation: • Ibrutinib	Without a del(17p)/*TP53* mutation: • **FCR**: The pivotal CLL14 trial population excludes patients who would normally be eligible for FCR.[1] The evidence submission is for FCR/BR-unsuitable patients • **BR**: According to the BSH guidelines on CLL (2018), BR is recommended as an alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions.[2] BR is not a comparator as the evidence submission is for FCR/BR-unsuitable patients only • **Chlorambucil with rituximab**: According to the BSH guidelines on CLL (2018), chlorambucil with rituximab is not routinely recommended[2] With a del(17p)/*TP53* mutation: • **Idelalisib with rituximab**: The clinical consensus is that ibrutinib has superseded idelalisib with rituximab as the B-cell-antigen receptor inhibitor (BCRi) of choice[2, 3] The scope presented in this submission has been clinically validated as

			representing current NHS practice by a panel of UK clinical experts (See Section B.1.3.4 and B.3.10)
Outcomes	• Overall survival • Progression- free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per final scope	The CLL14 trial collected data on each of these outcomes and the data presented in this submission is in line with the final scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per final scope and NICE reference case	As per final scope
Subgroups to be considered	• People with untreated CLL with del(17p)/*TP53* mutation • People with untreated CLL for whom fludarabine-based therapy is unsuitable • People with untreated CLL for whom bendamustine-based therapy is unsuitable	• People with untreated CLL with del(17p)/*TP53* mutation • People with untreated CLL for whom fludarabine-based therapy is unsuitable • People with untreated CLL for whom bendamustine-based therapy is unsuitable	The subgroups for consideration in the final scope are presented as the key population in the submission

Abbreviations: BCRi: B-cell-antigen receptor inhibitor; BR: bendamustine and rituximab; BSH: British Society for Haematology; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; NHS: National Health Service.
Source: Final Scope for ID1402[4]

B.1.2 *Description of the technology being appraised*

A description of the technology appraised is summarised in Table 3. The summary of product characteristics (SmPC) for venetoclax is provided in Appendix C.

Table 3: Technology being appraised

UK approved name and brand name	Venetoclax (Venclyxto®) [in combination with obinutuzumab]
Mechanism of action	Venetoclax is a first in class orally available, selective small molecule inhibitor of B-cell lymphoma 2 (Bcl2), an anti-apoptotic protein overexpressed in approximately 95% of CLL cases.[5-8] Venetoclax restores apoptosis independently of the p53 protein.[6, 8] As venetoclax is thought to act downstream of *TP53*, its mechanism of action provides a rationale for targeting Bcl2 irrespective of del(17p)/*TP53* status.[8]
Marketing authorisation/CE mark status	A marketing authorisation application for the indication of interest was submitted in [redacted]. Anticipated date of CHMP positive opinion is [redacted]. Marketing authorisation approval for venetoclax in this indication is anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Venetoclax currently has marketing authorisation from the European Medicines Agency (EMA)[9] in the following therapeutic indications: • Venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy • Venetoclax monotherapy is indicated for the treatment of CLL: o In the presence of del(17p) or *TP53* mutation in adult patients who are unsuitable for or have failed B-cell receptor pathway inhibitor; or o In the absence of del(17p) or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell pathway inhibitor The anticipated marketing authorisation wording for venetoclax in the indication of interest to this submission is: • Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)
Method of administration and dosage	Venetoclax is administered orally as a film coated tablet. The daily regimen is initiated on day 22 of Cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of Cycle 12. Obinutuzumab is administered intravenously for 6 cycles: • 100 mg on Day 1 and 900 mg on Day 2 (or 1000 mg on Day 1) of Cycle 1 • 1000 mg on Days 8 and 15 of Cycle 1 • 1000 mg on Day 1 of Cycles 2–6
Additional tests or investigations	Not applicable

List price and average cost of a course of treatment	Confirmed list price of venetoclax: • 14-tab pack (10 mg) = £59.87 (1 week, starting Day 22 Cycle 1, 20mg per day) • 7-tab pack (50 mg) = £149.67 (1 week, 50 mg per day) • 7-tab pack (100 mg) = £299.34 (1 week, 100 mg per day) • 14-tab pack (100 mg) = £598.68 (1 week, 200 mg per day) • 112-tab pack (100 mg) = £4,789.47 (Day 22 Cycle 2 until end of Cycle 12, 400 mg per day [28 days pack]) Confirmed list price of obinutuzumab: • 1000 mg = £3,312.00 At list price, the average cost of VenG for the course of 1-year when assuming 100% treatment compliance is £[redacted]
Patient access scheme (if applicable)	There is a simple discount patient access scheme (PAS) for venetoclax which entails providing a discount of [redacted] on the list price for venetoclax. The average cost of VenG for the course of 1-year, assuming 100% treatment compliance and accounting for this PAS is £[redacted] A confidential PAS is also available for obinutuzumab. (Note that the figure for the average cost of VenG above does not include the PAS price of obinutuzumab)

Abbreviations: Bcl2: B-cell lymphoma 2; CHMP: Committee for Medicinal Products for Human Use; CLL: chronic lymphocytic leukaemia; EMA: European Medicines Agency; PAS: Patient Access Scheme; SmPC: Summary of Product Characteristics; VenG: venetoclax with obinutuzumab.
Source: Venclyxto® SmPC;[9] Gazyvaro® SmPC.[10]

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 Disease overview and epidemiology

CLL is the most common of the chronic leukaemias, comprising 30% of all adult leukaemia.[11] CLL is a clonal disease of unknown aetiology, characterised by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow. The progressive accumulation of monoclonal B lymphocytes leads to leucocytosis, lymphadenopathy, hepatosplenomegaly, anaemia, thrombocytopenia, neutropenia, bone marrow failure, recurrent infections and systemic symptoms (fatigue, loss of appetite, weight loss, night sweats and shortness of breath when exercising).[12]

Recurrent genetic abnormalities (deletions or mutations) can be identified in the majority of cases of CLL. The disease is also genetically heterogeneous, and subject to clonal variation during the disease course with the emergence of treatment resistant sub-clones, especially following DNA damaging chemotherapy. Mutation of the tumour suppressor gene *TP53* (via deletion of the short arm of chromosome 17 (del[17p]), which contains *TP53*, or mutation of the *TP53* gene sequence) plays a critical role in cancer development and mediates resistance to chemotherapy.[13] *TP53* dysregulation is observed in 5–10% of untreated CLL patients,[14] and

patients with del(17p)/*TP53* mutation have been observed to have a much higher risk of rapid disease progression and a significantly reduced overall survival.[15, 16]

UK incidence of CLL (European-age standardised) for 2016 was recorded as 6.0 per 100,000 person years, with an estimated 3,412 new diagnoses in England and Wales (in 2016) and incidence is higher in male than female patients (1.7:1).[17-20] Survival of CLL patients is observed to be significantly shorter than that of the age-matched general population, for patients aged <55 years ($p<0.001$), 55–64 years ($p<0.001$), and 65–74 years ($p<0.001$) at CLL diagnosis; and a trend of shorter survival for those ≥75 years albeit not statistically significant ($p=0.136$).[21] CLL is a slowly progressive cancer with five-year relative survival rates of around 70% and 75% for men and women, respectively.[22] Overall, CLL accounts for around 1,000 deaths a year.[23]

Most patients are older than 70 years (median age at diagnosis is 72 years) and have clinically relevant coexisting conditions,[17, 24, 25] with more than 4 in 10 [42%] new cases being identified in patients aged 75 and over and the highest incidence rates being found in patients aged 85–89 for females, and 90+ for males.[19] Treatment of patients with comorbidities and high risk genetic subtypes (including *TP53* dysregulation) is an area of unmet need with a requirement to identify effective therapies with alternative mechanisms of action and acceptable side effect profiles.[26]

B.1.3.2 Disease burden

CLL develops slowly and, most often, patients with CLL are asymptomatic at the time of diagnosis and become aware of the disease following the detection of lymphocytosis in a routine blood count.[27]

Symptoms of CLL can include swollen lymph nodes; having frequent infections; severe sweating at night; weight loss; and breathlessness, tiredness and headaches due to anaemia.[27] Beyond the physical symptoms of the disease, CLL has a significant emotional impact too; the emotional wellbeing of CLL patients is significantly lower than the general population, and also significantly lower than patients with other cancer types.[28]

Fatigue is one of the most common symptoms of CLL,[29, 30] and the severity of fatigue is higher in CLL patients compared to published population norms and worsens as disease progresses.[28] The impact of disease progression and increased fatigue in CLL have both been shown to negatively impact the health-related quality of life (HRQoL) of patients.[28, 31] In the CLL14 trial, patients were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and results showed that disease progression had a negative impact across all 15 quality of life (QoL) domains and patient-reported HRQoL was most strongly correlated with fatigue as well as role functioning.[31] Consequently, as CLL progresses, it can also have an increasingly negative impact on patients' carers, as their requirements for care increase.[31]

CLL patients are at increased risk of other secondary cancers and greater risk of infections because CLL is a cancer of the B-lymphocytes, and consequently causes impairment to the immune system through impact of the disease on the glands of the lymphatic system, the spleen and other organs.[29, 32, 33] During the NICE appraisal committee meeting for TA429, patient experts described how the uncertainty associated with living with CLL greatly affects patients' QoL. They described how patients become isolated from family and friends to protect themselves from infection, preventing them from living a normal life, reducing their contribution to society and potentially shortening their life expectancy.[34]

Most patients with early stage CLL are not immediately treated, with treatment only being initiated once there is sufficient evidence of disease progression or disease-related symptoms.[35] Several studies have shown that treating patients with early-stage disease does not result in a survival benefit,[36-38] and while there is recent evidence from the CLL12 trial of a favourable delay in progression for patients with early stage disease treated with ibrutinib versus placebo,[39] current NHS practice is to take a 'watch and wait' approach to early treatment. Although there is evidence to support this approach, this 'watch and wait' period before treatment initiation can cause patients anxiety and emotional distress as they feel that 'nothing is being done'.[28] Additionally, once treatment has begun, it may often be extended over a long period of time, requiring prolonged emotional and practical support.[29]

Additional burden on patients stems from the impact of disease on their ability to work. CLL diagnosis may lead to temporary sick leave, a reduction in work hours or a need to ask for special adjustments at work, which could impact on their personal finances, causing an emotional burden.[29]

CLL is associated with a substantial economic burden, with recent evidence suggesting that costs associated with the disease are increasing over time.[40] Even in the early stages of the disease, a significant proportion of patients with CLL are hospitalised which is a key driver for costs to the healthcare system.[41, 42] Cumulatively, CLL leads to high lifetime costs for patients, the system and carers.[40, 43]

B.1.3.3 Minimal Residual Disease (MRD)

MRD describes the presence of a very small number of leukaemic cells remaining in the blood or bone marrow following treatment. Presence of undetectable MRD indicates the depth of remission. MRD can be measured in peripheral blood and bone marrow by highly sensitive molecular based assays or immunophenotyping. Currently, techniques for assessing MRD have become well standardised, with the six-colour flow cytometry (MRD flow), allele-specific oligonucleotide Polymerase Chain Reaction (ASO-PCR), and high-throughput sequencing using the ClonoSEQ assay being reliably sensitive down to a level below one CLL cell per 10,000 leukocytes (10^{-4} CLL cells per leukocyte). Patients will be defined as having undetectable MRD remission if they have blood or marrow with less than one CLL cell per 10,000 leukocytes. Measuring MRD in blood is easier and less painful for the patient and can generally be used for making this assessment, however it is less sensitive than testing the marrow, in particular in cases where therapies preferentially clear the blood but not the marrow (such as monoclonal antibodies). Therefore, it may be important to confirm that the marrow aspirate also has undetectable MRD when the blood is found to have undetectable MRD.[35]

Multiple studies have demonstrated that achieving MRD below 10^{-4} CLL cells per leukocyte in the blood and/or bone marrow (i.e. undetectable MRD) leads to an improved progression-free survival (PFS).[44]

In December 2015, the European Medicines Agency (EMA) has included undetectable MRD as an intermediate endpoint in a revision document to appendix 4 to the guideline on the evaluation of anticancer medicinal products in man. EMA states that *"undetectable MRD in patients with CLL in clinical complete remission (= MRD response rate) after induction therapy may be used as an intermediate endpoint for licensure in randomised well controlled studies designed to show superiority in terms of PFS"*.[45] In addition, based on studies reporting longer remission, improved overall survival (OS) and PFS for patients with undetectable MRD, the CLL guidelines of the

British Society for Haematology (BSH) present MRD as a factor which affects prognosis.[46] The importance of MRD in CLL is furthermore underscored by the publication of the updated International Workshop on CLL (iwCLL) guidelines in March 2018: According to the iwCLL update "*Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome*".[35]

B.1.3.4 Current UK CLL clinical pathway of care

CLL is diagnosed based on the combination of lymphocyte morphology, the detection of >5×10^9/L circulating clonal B cells persisting for greater than three months and a characteristic immunophenotype.[35] Additional investigations include cross-sectional imaging, bone marrow biopsy and cytogenetic analysis by fluorescent in-situ hybridisation (FISH). Testing of additional genetic biomarkers such as immunoglobulin heavy chain (*IGHV)* sequence, may be undertaken to assess the stage of disease and to provide additional prognostic information.[35] Disease is staged, most commonly in Europe, using the Binet system.[46, 47] With the increasing use of routine blood tests over time, the majority of patients are currently diagnosed with early stage disease.[48] More than 50% of CLL patients are asymptomatic at diagnosis and require no treatment. Symptoms appear as the disease progresses and treatment is initiated when a patient's disease becomes symptomatic or progressive (summarised as "active disease") as defined by iwCLL guidelines.[35]

Early intervention with chemotherapy does not improve the natural history of the disease and may drive clonal evolution and later treatment resistance and hence, therapy is only recommended for patients with rapidly progressive or symptomatic disease.[38, 49, 50] The time from diagnosis to treatment is variable according to the biological characteristics of the disease (for example the type of chromosomal deletions present or the presence of mutated *IGHV* sequence) although it is often greater than 5 years especially for patients with early stage disease.[51]

The aims of treatment are to achieve good quality remissions, leading to durable periods of PFS and to extend long-term OS whilst minimising side effects and toxicities from treatment.[46] Given the prognostic significance of achieving undetectable MRD and its relationship with longer periods of remission and survival,[52] undetectable MRD is now a key treatment goal for patients and clinicians.

Determining fitness status for chemotherapy

Due to the age distribution of CLL, two-thirds of patients are likely to have at least one significant co-morbidity and higher risk disease and this could impact on their fitness for chemotherapy.[53] As a result, an assessment of fitness status is required prior to initiating active treatment to ensure an appropriate choice for the patient. Unfortunately, the optimal strategy to determine fitness for chemotherapy remains undetermined and there is no agreement on the use of a specific formal co-morbidity assessment tool.[2] In routine clinical practice, assessment of fitness includes factors such as age, presence and severity of comorbidities and performance status.[2]

Treatment of previously untreated fit patients without del(17p)/*TP53* mutation

The BSH guidelines recommend fludarabine, cyclophosphamide and rituximab (FCR) as initial therapy for previously untreated, fit patients without *TP53* disruption, unless FCR is contraindicated due to comorbidities. Although there is no international consensus on a specific age restriction for FCR, elderly patients (>65 years old) are more likely to experience toxicity with intensive chemotherapy.[2]

The BSH guidelines also consider bendamustine and rituximab (BR) as an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions, e.g. renal impairment, more advanced age, concerns with marrow capacity or patient preference.[2] However, UK clinical experts at a recent AbbVie advisory board confirmed that there is limited use of BR in current NHS practice (estimated in <5% of untreated CLL patients).

It is worth noting that the population of relevance to this submission are patients who are unsuitable for FCR and BR since the eligibility criteria for the pivotal VenG CLL14 trial included patients with characteristics (e.g. coexisting conditions, cumulative illness rating scale [CIRS] score >6) that would typically make them unsuitable for FCR and BR.[1]

Treatment of previously untreated FCR/BR-unsuitable patients without del(17p)/*TP53* mutation

In patients considered unsuitable for FCR/BR, chlorambucil with obinutuzumab (GClb) is recommended by the BSH guidelines.[2] The BSH guidelines do not recommend chlorambucil with rituximab (RClb), and this combination is not approved by NICE; the guidelines note specifically that GClb showed significantly superior PFS and time-to-next treatment (TTNT) results when compared to RClb in the CLL11 study.[2, 54]

As a result, the standard of care therapy for FCR/BR-unsuitable CLL patients without del(17p)/*TP53* mutation is GClb, which is therefore the only relevant comparator in this population. This was validated by five clinical experts at an AbbVie-organised advisory board. The limited treatment options for these patients means that there is an unmet need for therapies with different mechanisms of action, particularly treatments which are tolerable to an elderly or FCR/BR-unsuitable population, and which provide a deep durable response. VenG has demonstrated significantly improved PFS and superior undetectable MRD results versus GClb in the CLL14 trial, which implies that fewer patients will require costly relapse therapies.[1] Furthermore, there is an unmet need for a chemotherapy-free treatment option which may reduce the risk of clonal evolution and treatment resistance.[26, 49] VenG also provides the same benefit of fixed duration treatment, which limits patient exposure and cost of therapy.

Treatment of previously untreated patients with del(17p)/*TP53* mutation

Ibrutinib is recommended as the treatment of choice for patients with untreated CLL and del(17p)/*TP53* mutation in the BSH guidelines and is also recommended by NICE for this indication.[2, 34] Of note is that ibrutinib was recommended in this indication, despite the absence of randomised trial data because of the high unmet need of the previously untreated del(17p)/*TP53* mutation subpopulation. The phase III RESONATE trial demonstrated ibrutinib efficacy versus ofatumumab in the relapsed/refractory setting and even though the trial did not include patients with untreated CLL, a simplifying assumption was made during the NICE appraisal "that the treatment effect in patients with a 17p deletion in the RESONATE trial who had previously had treatment (33% of patients) could be generalised to patients who had not had treatment".[34, 55] The NICE appraisal committee recognised that this simplifying assumption was associated with uncertainty. A follow-on trial, RESONATE 2, demonstrated ibrutinib superiority over chlorambucil in patients with untreated CLL, however the trial did not include any patients with the del(17p)/*TP53* mutation. In the CLL14 trial, VenG demonstrated a significantly improved PFS vs GClb in the del(17p)/*TP53* mutated subgroup.

Idelalisib and rituximab combination therapy is also approved by NICE in this indication,[56, 57] however idelalisib has more recently been associated with a higher risk of infection and death than the alternative therapies, leading to a review of its EMA license which now recommends idelalisib only for "first-line treatment of CLL in the presence of del(17p)/*TP53* mutation in patients who are not eligible for any other therapies".[57] Therefore, this combination has generally been superseded by ibrutinib.

Overall, ibrutinib is currently the standard of care in this subpopulation, however treatment options aside from ibrutinib are very limited and there is a high unmet need for patients who cannot tolerate ibrutinib, such as those with significant cardiac disease or bleeding risk. Recent data indicate that up to 41% of patients discontinue treatment with ibrutinib after a median of 7 months; of these patients, approximately 60% discontinue because of toxic effects.[58-63] As a result of this, it is of key importance to broaden the therapeutic options for the del(17p)/*TP53* population to those with a different mechanism of action from the B-cell receptor pathway inhibitors (BCRis; ibrutinib and idelalisib). In particular to include therapies which have demonstrated a deep durable treatment response in the del(17p)/*TP53* mutation population, such as venetoclax,[1, 64] and also for fixed duration therapies, which limits patient exposure as well as providing a reduced and more predictable treatment cost.

Table 3 below presents NICE recommended first-line treatments for CLL. It should be noted, however, that in current NHS practice, several NICE recommended medicines are no longer actively used, and any differences in the use of treatments in practice have been recorded below.

Table 4: NICE and BSH recommended first-line treatments for CLL

Treatment	Technical Appraisal ID	Population Restrictions	Use in clinical practice if different to NICE recommendations*	Relevance to this submission
Without del(17p)/*TP53* mutation – 'fit' patients				
Fludarabine, cyclophosphamide and rituximab (FCR)	TA174[65]			• The population of relevance to this submission are unsuitable for FCR and BR because the pivotal CLL14 trial on which this submission is based included patient characteristics (e.g. coexisting conditions, CIRS score >6) that would typically make them unsuitable for FCR and BR. • Clinical experts treating CLL patients in the UK NHS have confirmed that VenG would not be used in patients suitable for fludarabine or bendamustine-based therapies
Bendamustine (NB: the 2011 appraisal, TA216, was for bendamustine monotherapy, but subsequently bendamustine with rituximab [BR] has been used in clinical practice)	TA216[66]	• Patients for whom fludarabine combination chemotherapy is not appropriate	• The BSH guidelines recommend BR as an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions, e.g. renal impairment, more advanced age, concerns with marrow capacity or patient preference • However, clinical experts at an AbbVie organised HTA advisory board suggested that BR is a minority regimen, no longer routinely used in NHS practice, noting that BR has been shown to be inferior to the majority of CLL treatment options and therefore is only used in NHS practice in very specific circumstances	
Without del(17p)/*TP53* mutation – FCR/BR-unsuitable patients				
Chlorambucil with obinutuzumab (GClb)	TA343[67]	• Adults with comorbidities making full-dose fludarabine-based therapy unsuitable • Bendamustine-based therapy is unsuitable		• GClb is a relevant comparator to VenG in this population
Chlorambucil with or without rituximab	n/a		• Not recommended by NICE • This treatment has been shown to be inferior to GClb and as such is rarely used in practice	• RClb is not a relevant comparator in this submission as it is not recommended by NICE or in the BSH clinical guidelines[2]
With del(17p)/*TP53* mutation				
Ibrutinib	TA429[34]	• Chemo-immunotherapy is unsuitable		• Ibrutinib is a relevant comparator to VenG in this population

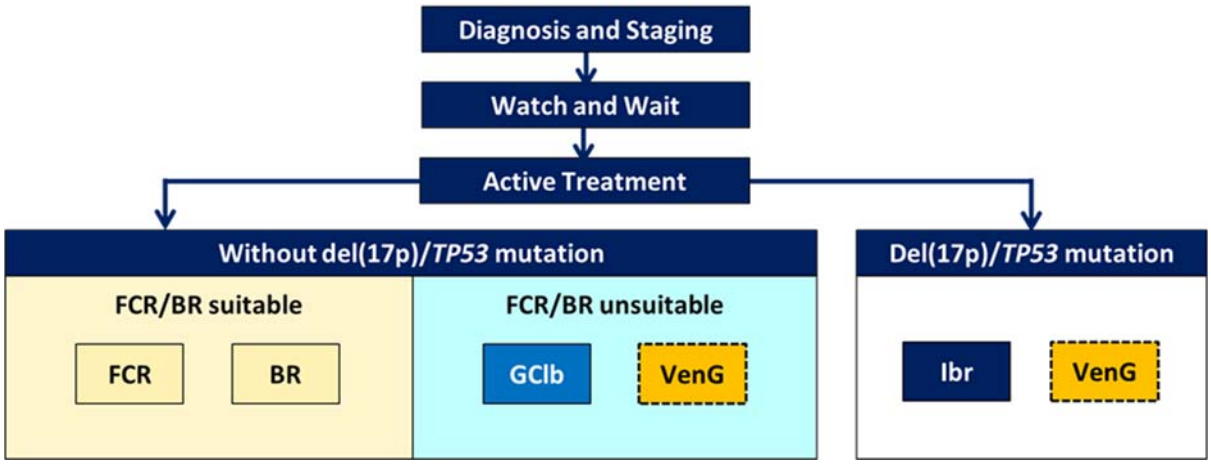
Treatment	Technical Appraisal ID	Population Restrictions	Use in clinical practice if different to NICE recommendations*	Relevance to this submission
Idelalisib with rituximab	TA359[56]		• Ibrutinib has superseded idelalisib with rituximab as the BCRi of choice	• Treatment with idelalisib with rituximab has been superseded by ibrutinib due to its high risk of infection, as noted specifically in the BSH guidelines, and therefore is not a comparator in this submission[2]

*validated by a panel of clinical experts at an AbbVie organised HTA advisory board
Abbreviations: BCRi: B-cell receptor pathway inhibitor; BSH: British Society for Haematology; CIRS: cumulative illness rating scale; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; GClb: obinutuzumab with chlorambucil; HTA: health technology assessment; NHS: National Health Service; RClb: chlorambucil with rituximab; VenG: venetoclax with obinutuzumab.
Source: National Institute for Health and Care Excellence Guidance;[34, 56, 65-69] Schuh et al. 2018.[2]

B.1.3.5 Proposed position of VenG in clinical practice

Figure 1 presents a simplified version of the clinical pathway of care for adult patients with CLL, along with the proposed position of VenG. The pathway takes into account NICE guidance and guidelines published by the British Society for Haematology (BSH).[2, 34, 56, 65-68] This simplified clinical pathway was validated by a panel of five UK clinical experts (all members of the UK CLL Forum) at an AbbVie-organised HTA advisory board in April 2019.

Figure 1: CLL treatment pathway in current NHS clinical practice and proposed positioning of VenG



Abbreviations: BR: bendamustine and rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; GClb: obinutuzumab and chlorambucil; Ibr: ibrutinib; NHS: National Health Service; VenG: venetoclax and obinutuzumab.
Source: National Institute for Health and Care Excellence Guidance[34, 56, 65-68]; Schuh et al. 2018.[2]

As depicted in the pathway in Figure 1, the anticipated positioning of VenG is:

- For the treatment of previously untreated FCR/BR-unsuitable patients without del(17p)/*TP53* mutation
- For the treatment of previously untreated patients with del(17p)/*TP53* mutation

The anticipated marketing authorisation is "Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)". This broad label includes patients who would be eligible for FCR and BR, however, it is likely that in NHS practice, VenG will be used in line with the CLL14 study (see Section B.2 for more detail), in which patients were required to have coexisting conditions (a total CIRS score of 6 or more, or creatine clearance (CrCl) <70 mL/min),[1] therefore the majority of the trial population would be considered unsuitable for FCR or BR. This assumption was agreed by consensus among the five UK clinical experts (UK CLL Forum members) consulted at the HTA advisory board.

This submission is aligned with the anticipated positioning of VenG within the UK NHS treatment pathway. Based on the proposed positioning of VenG in clinical practice, the appropriate comparators are GClb, in FCR/BR-unsuitable patients without del(17p)/*TP53* mutation, and Ibr, in patients with del(17p)/*TP53* mutation.

Unmet treatment need

CLL incidence rates increase with age.[19, 25] As a result of the current demographic changes associated with an aging population, the prevalence and mortality of CLL are likely to increase over the next decades, increasing the burden of disease on the NHS.

There are limited treatment options available for untreated CLL, with even fewer options for patients with del(17p)/*TP53* mutation compared to patients without del(17p)/*TP53* mutation. Chlorambucil based chemo-immunotherapies are the backbone of treatment in FCR/BR-unsuitable patients without del(17p)/*TP53* mutation, however there is an unmet need for a broader range of therapeutic options with a different mechanism of action,[2] particularly those with a safety profile suitable for an elderly, comorbid population that are not suitable for FCR/BR.

While B cell receptor inhibitors (BCRis) such as ibrutinib have reduced the reliance on toxic chemo-based therapies in the previously untreated del(17p)/*TP53* mutation population, there is an unmet need for patients who cannot tolerate ibrutinib, such as those with cardiac risk factors.[2] Furthermore, BCRis, such as ibrutinib, are associated with an indefinite treatment period due to their treat-to-progression dosing schedule, and have not demonstrated high rates of undetectable MRD.

There is a high unmet need for therapies improving PFS, that are effective in both subpopulations with del(17p)/*TP53* mutation and without del(17p)/*TP53* mutation and that demonstrate potential to achieve undetectable MRD, which suggests a deep, durable response to treatment. There are also benefits to patients, clinicians and the NHS if these can be achieved with a chemo-free fixed treatment duration.

CLL14 was a randomised, open label, phase III trial, which demonstrated that VenG has the potential to meet this high unmet need in untreated CLL: offering a highly effective treatment of fixed duration with manageable toxicity, improvement in PFS and high rates of undetectable MRD. After a median follow-up period of 28.1 months, the rate of investigator-assessed PFS was significantly higher in the VenG group (30 events in 216 patients including 14 with progressive disease [PD] and 16 deaths due to fatal adverse events [AEs], most likely not associated with treatment but patient comorbidities) when compared to the GClb group (77 events in 216 patients including 69 PDs and 8 deaths due to fatal AEs); (hazard ratio [HR] for progression or death 0.35; 95% CI: 0.23, 0.53; p<0.001). Furthermore, the benefit was maintained across major clinical and biologic subgroups, including the subgroups with and without del(17p)/*TP53* mutation; the 2-year rate of PFS among patients with del(17p)/*TP53* mutation was 73.9% in the VenG group versus 32.7% in the GClb group (HR 0.31, 95% CI: 0.13, 0.76). A higher proportion of patients in the VenG arm when compared to the GClb arm also achieved undetectable MRD at end of treatment (EOT) in both the peripheral blood (75.5% vs 35.2%, p<0.001) and in the bone marrow (56.9% vs 17.1%, p<0.001), and this result remained in favour of VenG throughout the study period. The benefit of VenG over GClb was confirmed by an independent review committee (IRC) assessment of PFS and other secondary efficacy end points.[1]

In conclusion, the CLL14 trial provides evidence that VenG is an effective treatment in both patients with and without del(17p)/*TP53* mutation, providing a cost-effective and valuable alternative to current first-line treatment options. Furthermore, VenG has the potential to provide substantial health-related benefits in the form of a fixed-treatment duration chemo-free therapy,

with a manageable side effect profile. This enables a significant proportion of patients prolonged time without therapy, reducing their exposure, and the overall cost burden of treatment.

B.1.4 *Equality considerations*

No equality issues are presented by venetoclax.

B.2 Clinical effectiveness

A systematic literature review (SLR) identified one randomised controlled trial (RCT) for VenG in the relevant patient population as defined by the NICE scope (CLL14)

- The results of the CLL14 trial, including data for patient-reported HRQoL outcomes, are presented from the Fischer et al. publication[1] and the clinical study report (CSR).[70]
- The primary outcome was investigator-assessed progression-free survival (PFS), which was supported by assessment from an Independent Review Committee (IRC).
- Secondary outcomes included overall response rate (ORR), complete response (CR), MRD response rate in peripheral blood and bone marrow, overall survival (OS), event-free survival (EFS), time to next treatment (TTNT), HRQoL and safety (treatment-emergent adverse events [TEAEs]).
- CLL14 was methodologically robust and considered to be at low risk of bias.
- The results of the CLL14 study are well aligned with the decision problem specified in the NICE scope and the trial results are directly relevant to treatment in NHS clinical practice.

The CLL14 trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS, assessed by both investigators and IRC

- Treatment with VenG resulted in statistically significant and clinically meaningful prolongation of PFS when compared with GClb treatment (HR 0.35; 95% CI: 0.23, 0.53; p<0.001).
- The IRC-assessed PFS results further validated the primary endpoint (HR 0.33; 95% CI: 0.22, 0.51; p<0.0001, stratified log-rank test).
- The benefit was maintained across major clinical and biologic subgroups, including high-risk patients such as those with del(17p)/*TP53* mutation, which were consistent with the primary analysis.
- At the end of treatment assessment, a higher proportion of patients in the VenG arm (183 of 216, 84.7%) achieved an overall response, considering complete response (CR), incomplete bone marrow recovery (CRi), or partial response (PR) compared to the GClb arm (154 of 216, 71.3%) and the difference was statistically significant (p<0.001).
- VenG treated patients achieved a higher rate of combined response: CR/CRi (49.5%) compared with GClb treated patients (23.1%) and the difference in response rate (26.4; 95% CI: 17.4, 35.4; p<0.001) is both statistically significant and clinically meaningful.
- A higher proportion of patients in the VenG arm when compared to the GClb arm achieved undetectable MRD at EOT (three months after treatment completion) in both peripheral blood (75.5% vs 35.2%, p<0.001) and in bone marrow (56.9% vs 17.1%, p<0.001). The result remained in favour of VenG throughout the study period, during the fixed duration treatment and off-treatment during follow-up.
- Median OS was not reached in either arm. The data are too immature to be meaningful (<10% of enrolled patients had died), due to the first-line position of treatment and the natural history of CLL, and therefore are not interpretable at this time. Further planned data-cuts of CLL14 may reduce uncertainty in OS estimates.
- Overall results of patient reported outcome (PRO) assessments were comparable in the VenG and GClb arms with patients reporting no impairment to baseline functioning, global health status or quality of life (QoL) during treatment and follow-up, and no increase in symptom burden and interference. The results suggest that the combination of VenG did not adversely impact health-related quality of life (HRQoL) in previously untreated CLL patients; as such, VenG provided a much deeper response and superior PFS without resulting in a reduction in HRQoL.
- Overall, the results of the CLL14 trial clearly demonstrate the clinical efficacy of VenG compared with GClb in patients with previously untreated CLL, in a population with coexisting medical conditions, with a meaningful delay in PFS and significantly higher rates of undetectable MRD.

For the population of patients with del(17p)/*TP53* mutation, unadjusted naïve indirect comparisons to ibrutinib demonstrated no statistically significant benefits for either treatment

- An SLR identified four publications that presented data for ibrutinib in a del(17p)/*TP53* population.
- A feasibility assessment determined there was insufficient data on CLL patients receiving ibrutinib as first-line treatment to allow for a matching-adjusted indirect comparison (MAIC).
- Unadjusted HRs between ibrutinib and VenG were calculated as [redacted] for PFS (p=[redacted]; 95% CI: [redacted]), and [redacted] for OS (p=[redacted]; 95% CI: [redacted]), however none of the results were statistically significant due to the small population sizes of the studies included in the analysis.

The results demonstrated VenG to be tolerable, with an acceptable AE profile, compared with GCIb

- The overall frequency of AEs of any grade was higher in the GCIb arm (213 patients [99.5%]) compared with the VenG arm (200 [94.3%]) and comparable between treatment arms for Grade 3 or 4 AEs (164 [76.6%] and 167 [78.8%], respectively).
- The overall incidence of deaths due to any cause was generally comparable (17 deaths in the GCIb arm compared with 20 in the VenG arm). The frequency of fatal AEs was numerically higher in the VenG arm, but analysis showed a causal association with study drug appeared unlikely, due to the long latency period from the last study drug, relevant pre-existing medical conditions and concomitant comorbidities or risk factors.
- The safety profile associated with VenG therapy is consistent with the established safety profiles of venetoclax and obinutuzumab. Toxicity is predictable and manageable in the population studied.

Venetoclax is a first-in-class, oral treatment, with a unique targeted mechanism of action, offering a valuable alternative to current first-line treatment options

- VenG prolongs PFS and has the potential to provide substantial health-related benefits in an indication with limited treated options.
- VenG has demonstrated the ability to induce deep, durable responses to treatment, in the form of a fixed-treatment duration chemo-free therapy with a manageable side effect profile, enabling a significant proportion of patients prolonged time without therapy, reducing their risk of cumulative toxicity or mechanism induced drug-resistance, and reducing the overall cost burden of treatment.

B.2.1 *Identification and selection of relevant studies*

- A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy, effectiveness, safety and tolerability of treatments for untreated CLL
- A broad SLR was conducted, capturing all available treatments for previously untreated CLL, and 150 publications, reporting on 116 unique studies were identified (36 RCTs and 80 non-RCT)
- Of these studies, one study, CLL14, presented relevant data to inform the comparison between VenG and GCIb in an FCR/BR-unsuitable population without del(17p)/*TP53* mutation
- Of the four publications identified in the SLR which presented data for Ibr monotherapy as first-line treatment in CLL patients with del(17p)/*TP53* mutation,[60, 71-73] two studies were selected for a feasibility assessment to conduct a MAIC for comparison between VenG and Ibr in

patients with del(17p)/*TP53* mutation: a multicentre, retrospective cohort study (Mato et al. 2018), and a phase 2, open-label study (Farooqui et al. 2015 and Ahn et al. 2018 report the same study).[60, 71-73] A MAIC was deemed infeasible and therefore an unadjusted naïve indirect comparison was conducted using real-world data from Mato et al.[60] The Mato[60] study was used to inform the comparison between VenG and Ibr. The Ahn study was tested in a scenario analysis

- Full details of the SLR search strategy, methodology and results can be found in Appendix D, along with details of the indirect comparisons conducted

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified only one RCT (CLL14) for venetoclax in combination with obinutuzumab in previously untreated CLL patients.

CLL14 was an open-label, parallel, multicentre, phase III, RCT investigating the efficacy, safety and tolerability of fixed-duration treatment with venetoclax in combination with obinutuzumab (VenG), versus fixed duration treatment with chlorambucil in combination with obinutuzumab (GClb), in patients with previously untreated CLL and coexisting medical conditions.[1]

Data from CLL14 has been published in the New England Journal of Medicine by Fischer et al.,[1] and additional information is also available from the CLL14 Clinical Study Report.[70]

A summary of the clinical effectiveness evidence from the CLL14 trial is presented in Table 5.

Table 5: Clinical effectiveness evidence

Study	CLL14		
Trial primary reference	Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. New England Journal of Medicine 2019;380:2225-2236		
Study design	Open label, parallel, multicentre, phase III, randomised controlled trial (RCT)		
Population	Patients with previously untreated CLL and coexisting medical conditions		
Intervention(s)	Venetoclax in combination with obinutuzumab		
Comparator(s)	Chlorambucil in combination with obinutuzumab		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	The CLL14 trial is the only RCT assessing venetoclax in combination with obinutuzumab in the relevant indication, and therefore represents the primary source of clinical effectiveness data. This trial informed the marketing authorisation application and considers a population directly relevant to the decision problem addressed in this submission.		
Reported outcomes specified in the decision problem	• **Independent review committee (IRC)-assessed progression-free survival (PFS)** • Investigator-assessed PFS • Investigator-assessed overall response-rate • Investigator-assessed complete response-rate • Overall survival • **Adverse effects of treatment** • **Health-related quality of life**		
All other reported outcomes	• **MRD response rate measure by ASO-PCR (peripheral blood and bone marrow)** • Duration of response • Event-free survival • **Time-to-next treatment**		

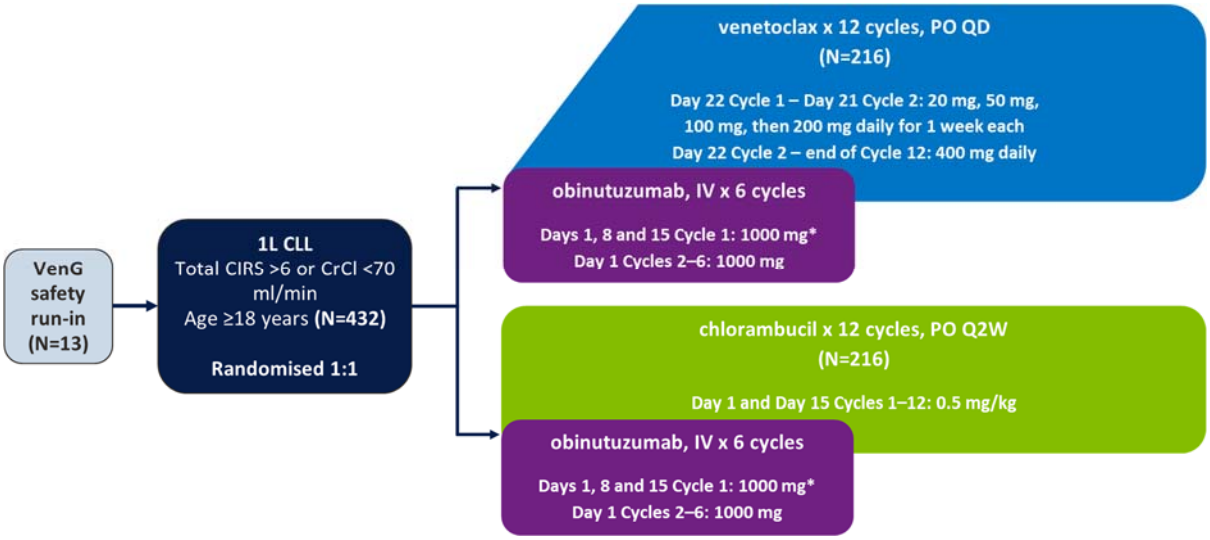
Outcomes in **bold** indicate those used in the economic model.
Abbreviations: ASO-PCR: allele-specific oligonucleotide polymerase chain reaction; CLL: chronic lymphocytic leukaemia; IRC: independent review committee; MRD: minimal residual disease; PFS: progression-free survival; RCT: randomised controlled trial.
Source: Fischer et al. 2019[1], AbbVie Data on File (CLL14 Clinical Study Report)[70]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

An overview of the study design is presented in Figure 2.

Figure 2: Overview of the study design for CLL14



*For the first dose of obinutuzumab on Day 1 Cycle 1, this can be given as either 1000 mg on Day 1 or as 100 mg on Day 1 and 900 mg on Day 2.
1 Cycle = 28 days.
Abbreviations: CIRS: cumulative illness rating scale; CLL: chronic lymphocytic leukaemia; CrCl: creatinine clearance; IV: intravenous; PO: oral; QD: once daily; Q2W: once every two weeks; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1]

B.2.3.2 Eligibility criteria

A brief summary of the eligibility criteria for CLL14 are presented in Table 6. The full eligibility criteria can be found in Appendix L.

Table 6: Summary of eligibility criteria for CLL14

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Life expectancy > 6 months • Documented previously untreated CLL according to the iwCLL criteria[35] • CLL that requires treatment according to the iwCLL criteria[35] • Total CIRS score >6 or CrCl <70 mL/min	• Inadequate renal function: CrCl <30 mL/min • History of confirmed progressive multifocal leukoencephalopathy or prior malignancy • Pregnant women and nursing mothers

Abbreviations: CIRS: cumulative illness rating scale; CLL: chronic lymphocytic leukaemia; CrCl: creatinine clearance; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia.
Source: Fischer et al. 2019.[1]

B.2.3.3 Summary of CLL14 methodology

A summary of the methodology of CLL14 is available in Table 7.

Table 7: Summary of CLL14 trial methodology

Location	International, multicentre trial conducted in 21 countries: Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Italy, Mexico, New Zealand, Poland, Romania, Russia, Spain, Switzerland, **United Kingdom**, and United States
Trial Design	• Prospective, open-label, randomised phase III study • Initially, a 12-patient non-randomised safety run-in phase of VenG was conducted (an additional 13th patient was enrolled following a withdrawal). After the 12th venetoclax-treated patient had reached the end of Cycle 3, a formal review by the Sponsors, the German CLL Study Group and the independent Data Monitoring Committee (iDMC) confirmed no stopping criteria (one treatment-related death or one Grade 4 AE related to a clinical TLS) had been met and the Sponsors proceeded with randomisation into the trial • Eligible patients were randomised in a 1:1 ratio to one of the two treatment arms (VenG or GClb) through a block stratified randomisation procedure. Randomisation was performed by IVRS • Randomisation was stratified with regards to: o Binet stage: A, B or C o Geographic region: US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America • CLL14 was an open-label study. However, the Sponsors were blinded to treatment allocation during IVRS randomization and assessments by the IRC were blinded to treatment arm. The iDMC reviewed unblinded safety data by treatment arm (which was prepared by an independent data coordinating centre to preserve blinding and prevent bias) for the purpose of interim safety reviews and the planned interim analyses of efficacy. The Sponsors and study team did not have access to the unblinded information reviewed by the iDMC
Eligibility criteria for participants	People with previously untreated CLL according to the iwCLL criteria A brief summary of the eligibility criteria for CLL14 are presented in Table 6. The full eligibility criteria can be found in Appendix L.
Settings and locations where the data were collected	International (196 study locations in 21 countries): Argentina (1 participant), Australia (46), Austria (6), Brazil (22), Bulgaria (33), Canada (13), Croatia (12), Denmark (21), Estonia (5), France (39), Germany (54), Italy (26), Mexico (3), New Zealand (18), Poland (16), Romania (7), Russian Federation (41), Spain (30), Switzerland (3), **United Kingdom (8 across 6 sites)**, United States (28)
Trial drugs	• VenG arm (N=216): o *Venetoclax:* ramp up starting Day 22 Cycle 1 to Day 21 Cycle 2 (dose ramp-up period: 20 mg, 50 mg, 100 mg, then 200 mg daily for 1 week each); 400 mg daily Day 22 Cycle 2 to end of Cycle 12 ▪ Venetoclax was administered orally and at home. The 20 mg and 50 mg doses were administered in hospital for patients at high risk of TLS

	o *Obinutuzumab:* 1000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6 (every 28 days) ▪ Obinutuzumab was administered by IV infusion. The first dose (1000 mg) of obinutuzumab drug administration could be split over 2 days (100 mg on Day 1 and 900 mg on Day 2). Overnight hospitalisation could be required on Day 1 of Cycle 1 following the first infusion of obinutuzumab • GClb arm (N=216): o Chlorambucil: 0.5 mg/kg Day 1 and Day 15 Cycles 1–12 (every 28 days) ▪ Chlorambucil was administered orally o Obinutuzumab: 1000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6 (every 28 days) ▪ As above, obinutuzumab was administered by IV infusion. The first dose (1000 mg) of obinutuzumab drug administration could be split over 2 days (100 mg on Day 1 and 900 mg on Day 2). Overnight hospitalisation could be required on Day 1 of Cycle 1 following the first infusion of obinutuzumab • Venetoclax dosing for this study was based on the phase I dose-escalation study M12-175, which examined single-agent venetoclax in relapsed and refractory patients with CLL and NHL[74] • Obinutuzumab dosing was based on the approved dose for first-line treatment • Chlorambucil dosing for this study was based on the findings from the GCLLSG CLL5 trial[75]
Permitted and disallowed concomitant medication	Concomitant medication included any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 30 days prior to the screening period. Patients who were using oral contraceptives, hormone-replacement therapy, or other maintenance therapy were to continue their use. **Excluded therapies:** • Anticancer therapies, including chemotherapy, radiotherapy, or other investigational therapy (which included targeted small molecule agents): Excluded 5 half-lives prior to first dose and throughout venetoclax administration. • Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent: Excluded 8 weeks prior to first dose of study drug. • Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids. • Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit: Excluded 3 days prior to first dose and throughout venetoclax administration. **Excluded during the venetoclax ramp-up period and cautionary thereafter:** • Strong and moderate CYP3A inhibitors: Excluded during the venetoclax ramp-up period; alternative medications considered.

	o If a patient required use of these medications while they were receiving 400 mg per day of venetoclax, they were to be used with caution and the venetoclax dose was reduced 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, 3 days were to have elapsed before venetoclax dose was increased back to the target dose. • Strong and moderate CYP3A inducers: Excluded during the venetoclax ramp-up period; alternative medications considered. o If a patient required use of these medications while receiving 400 mg per day of venetoclax, they were to be used with caution and the Medical Monitor contacted for guidance. **Cautionary therapies:** • Warfarin • Weak CYP3A inducers or inhibitors • P-gp substrates or inhibitors • BCRP substrates or inhibitors • OATP1B1/1B3 substrates or inhibitors
Primary outcomes	The primary efficacy outcome measure for the CLL14 trial was as follows: • PFS, defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. Disease progression and relapse were assessed by the investigators using the iwCLL criteria
Other outcomes use in the economic model/specified in the scope	All efficacy and safety, and patient recorded outcomes (PROs), were pre-specified. <u>Efficacy</u> • PFS based on IRC-assessments, defined as the time from randomisation to the first occurrence of progression or relapse or death from any cause • ORR (defined as rate of a clinical response of CR, CRi, or PR) at the completion of treatment assessment, as determined by the investigator according to the iwCLL guidelines • Combined response (defined as a clinical response of CR or CRi) at the completion of treatment assessment, as determined by the investigator according to the iwCLL guidelines • MRD response rate (determined as the proportion of patients with undetectable MRD) measured in the peripheral blood at the completion of treatment assessment and MRD response rate as measured in the bone marrow at the completion of treatment, both measured by ASO-PCR • ORR at completion of combination treatment response assessment (Cycle 7, Day 1 or 28 days after last IV infusion)

	• MRD response rates in the peripheral blood and bone marrow at completion of combination treatment assessment (Cycle 9, Day 1 or 3 months after last IV infusion), both as measured by ASO-PCR • OS, defined as the time between the date of randomization and the date of death due to any cause • Duration of overall response, defined as the time from the first occurrence of a documented overall response to the first occurrence of progression or relapse as determined by the investigator or death from any cause • Event-free survival (EFS), defined as the time between date of randomization and the date of disease progression/relapse on the basis of investigator-assessment, death, or start of a new anti-leukemic therapy • Time to next anti-leukemic treatment, defined as time between the date of randomisation and the date of first intake of new anti-leukemic therapy or death from any cause Safety • Nature, frequency, and severity of adverse events and serious adverse events • Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment • Lymphocyte immunophenotyping and incidence of human−anti-human antibodies • Premature withdrawals PROs The PRO measures for this study are as described below. The first assessment was completed during the first obinutuzumab infusion, and PROs will be followed until end of study as defined by 5 years after the last randomised patient: • To evaluate changes following treatment in disease and treatment-related symptoms in MDASI-CLL scores • To evaluate changes in role functioning and global health status/QoL scales following treatment with the EORTC QLQ-C30 Health Economic Outcome • EQ-5D-3L questionnaire Exploratory Outcomes • MRD, measured using new technologies, including flow cytometry and next-generation sequencing; undetectable MRD defined using a cut-off of 10^{-4} (less than 1 cell in 10,000 leukocytes) for comparison with ASO-PCR, and secondly by the limit of sensitivity of each of the above technologies • Relationship between MRD and PFS on the basis of peripheral blood assessed using ASO-PCR • Relationship between various baseline markers and clinical outcome parameters in patients from both arms of the

	study (including but not limited to CLL FISH [17p-, 11q-, 13p-, + 12q], *IGHV* mutation status, *TP53* mutation status, serum parameters, Bcl2 expression, and other CLL disease markers)
Pre-planned subgroups	• Binet stage at screening (A, B, C) • Geographic region (US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America) • Age (<75, ≥75) • Gender (male, female) • Cytogenetic factors (deletion 17p, 11q and 13q, trisomy 12) • *TP53* status (deletion and/or mutation, none) • *IGHV* mutational status (unmutated, mutated)

Abbreviations: AE: adverse event; ASO-PCR: allele-specific oligonucleotide polymerase chain reaction; Bcl2: B-cell lymphoma 2; BCRP: breast cancer resistant protein; CLL: chronic lymphocytic leukaemia; CR: complete response; CRi: complete response with incomplete bone marrow recovery; CRR: complete response rate; CYP3A: cytochrome P4503A; EFS: event-free survival; EORTC QLQ-C30; European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version; FISH: fluorescence in situ hybridisation; GClb: chlorambucil with obinutuzumab; GCLLSG: German Chronic Lymphocytic Leukaemia Study Group; iDMC: independent Data Monitoring Committee; *IGHV*: immunoglobulin heavy-chain variable region; IRC: independent review committee; IV: intravenous; IVRS: interactive voice response system; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; MDASI: MD Anderson Symptom Inventory: MRD: minimal residual disease; NHL: non-Hodgkin's lymphoma; OATP: organic-anion-transporting polypeptide; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; P-gp: P-glycoprotein; PR: partial response; PRO: patient-reported outcome; QoL: quality-of-life; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019, [1] AbbVie Data on File (CLL14 Clinical Study Report)[70]

Reliability and validity of endpoints

The reliability, validity and current use of each outcome reported in the CLL14 trial in clinical practice is provided in Table 8.

Table 8: Reliability/validity/current use of clinical endpoints in practice

Outcome	Reliability/validity/current use in clinical practice
Primary endpoint	
PFS	PFS is used in clinical practice and is an important measure of disease control. However, PFS is affected by the timing of assessments and can be prone to investigator bias unless strict criteria for response evaluation are used, as were implemented in the CLL14 trial.
Secondary endpoint	
OS	OS is the gold standard endpoint for studies in cancer. Death is definitive, is easily compared across disease sites and is not subject to investigator bias.
Response rate	Response rate provides an indication of the patients who will benefit from treatment. Not all patients who respond to treatment will benefit from treatment, but patients must have an initial response in order to demonstrate benefit from treatment.
MRD	MRD testing is a sensitive methodology for the detection of very small numbers of cancer cells and represents a robust measure of assessing quality of response to treatment.
Duration of response	Measures the period over which treatment response is maintained, in patients who initially achieve a response. Given the fixed duration treatment in CLL14 this demonstrates the ability of treatment to drive a prolonged response even after treatment cessation.
TTNT	TTNT is defined as the time from randomisation to start of new non-protocol anti-CLL therapy or death from any cause, it is easily compared across disease sites and can provide an endpoint meaningful to patients given the incurable nature of CLL.
PROs and HRQoL	PROs and HRQoL are important measures given the incurable nature of CLL.

Abbreviations: CLL: chronic lymphocytic leukaemia; HRQoL: health-related quality of life; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; PRO: patient reported outcome; TTNT: time-to-next treatment.

B.2.3.4 Baseline characteristics

The randomised phase of the CLL14 study was opened in August 2015 and completed recruitment of 432 patients in August 2016. Patients were randomly assigned in a 1:1 ratio to receive either VenG or GClb with the use of a Web and voice mail system based on a computer-generated randomisation schedule. A block size of six was used to balance the randomization. Patients were stratified according to Binet stage and geographic region.

The baseline characteristics of patients included in the CLL14 trial are summarised in Table 9; the full table of baseline characteristics can be found in Appendix L. A total of 432 patients were randomised to VenG (n=216) or GClb (n=216). Patient characteristics at baseline were well balanced between treatment groups. The patients had a median age of 72 years (range: 41–89 years) and most patients were male (66.9%), reflective of the fact that CLL is more common in men than women.[19]

Overall, the median time from first diagnosis of CLL to randomisation was 2.5 years (0–20.4 years). The majority of patients were Binet stage B or C (79.1%) at baseline and approximately half (49.8%) were experiencing B symptoms (defined as unintentional weight loss [10% or more within 6 months]; significant fatigue [European Cooperative Oncology Group (ECOG) performance status 2 or worse]; fevers [>38.0°C for ≥2 weeks without evidence of infections]; or night sweats [for >1 month without evidence of infection]).

The median CIRS score was 8 (0–28), and the median creatinine clearance was 66.4 mL/min (0.1–3,670.0 mL/min). Altogether, 13.8% of the patients had *TP53* deletion, mutation, or both and 59.8% had unmutated *IGHV*. With regard to the risk of tumour lysis syndrome (as measured by the diameter of the largest lymph node by radiological assessment or absolute lymphocyte count), 13.4%, 64.4%, and 22.2% of the patients in the VenG group were at low, medium, and high risk, respectively. These risk categories were balanced between groups; 19.9% in the GClb arm and 22.2% in the VenG arm belonged to the high-risk category.

In terms of prognosis, the CLL-International Prognostic Index (IPI) scores were similar for the two treatment arms; 60.0% of patients in the GClb arm and 60.4% in the VenG arm had a high score and 28.0% and 25.7%, respectively, had an intermediate score.

Table 9: Summary of CLL14 patient baseline characteristics

Characteristic	VenG (N= 216)	GClb (N= 216)
Age ≥75 years, n (%)	72 (33.3)	78 (36.1)
Male sex, n (%)	146 (67.6)	143 (66.2)
Median time from diagnosis, months (range)	31.2 (0.4–214.7)	29.2 (0.3–244.8)
Binet stage, n (%)		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumour lysis syndrome risk category, n (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6, n (%)	186 (86.1)	177 (81.9)
Estimated CrCl <70 ml/min, n/N (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup, n/N (%)*		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)

No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status, n/N (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status, n/N (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)
TP53 deleted and/or mutated, n (%)	24/172 (14.0)	22/161 (13.7)

*Cytogenetic subgroups were determined according to the hierarchical model of Döhner et al.[15]
Abbreviations: CIRS: cumulative illness rating scale; CrCl: creatinine clearance; GClb: chlorambucil with obinutuzumab; *IGHV*: immunoglobulin heavy-chain variable region gene; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019. [1]

B.2.3.5 Concomitant medications

The therapeutic classes of concomitant medications used by more than [redacted] of all patients in the safety population were analgesics ([redacted] patients [redacted]%]), antihistamines ([redacted] patients [redacted]%]), and steroids ([redacted] patients [redacted]%]). These medications were included as prophylaxis for infusion-related reactions at the first administration of obinutuzumab.

A similar percentage of patients received granulocyte-colony stimulating factor (G-CSF) as prophylaxis for neutropenia during the study between the two arms ([redacted] patients [redacted]%] in the GClb arm compared with [redacted] [redacted]%] in the VenG arm). A similar proportion of patients received treatment for the indication of neutropenia ([redacted] [redacted]%] compared with [redacted] [redacted]%]). By treatment period, use of GCSF was [redacted] during the combination treatment period.

The following classes had a difference of >5% between arms: antidiarrheals ([redacted] patients [redacted]%] in the GClb arm compared with [redacted] [redacted]%] in the VenG arm); blood, blood components, and substitutes ([redacted] [redacted]%] compared with [redacted] [redacted]%], respectively); general anaesthetics ([redacted] [redacted]%] compared with [redacted] [redacted]%], respectively); and laxatives and stool softeners ([redacted] [redacted]%] compared with [redacted] [redacted]%], respectively).

B.2.3.6 Concurrent Diseases

A concurrent medical condition at baseline was reported in [redacted] (in the GClb group), reflecting the co-morbid patient population enrolled.

Vascular disorders were the most frequent type of concurrent medical condition, with fewer patients in the GClb arm having such a condition ([redacted] [redacted]%] compared with [redacted] [redacted]%] in the VenG arm). The difference was driven by hypertension. Other frequently reported medical conditions (in >30% of patients overall and balanced between arms) are presented in Table 10.

Imbalances were present for respiratory, thoracic and mediastinal disorders, with the difference largely driven by chronic obstructive pulmonary disease (COPD) and asthma, and for psychiatric disorders, with the difference largely driven by insomnia. The data for these concurrent conditions are presented in Table 10.

Table 10: Concurrent medical conditions at baseline

Concurrent Disease	VenG, n (%)	GClb, n (%)
Frequently reported concurrent conditions (>30% of patients overall)		
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypercholesterolemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Imbalanced concurrent conditions		
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
COPD	[redacted]	[redacted]
Asthma	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]

Abbreviations: COPD: chronic obstructive pulmonary disease; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)[70]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

All patients were analysed according to the treatment group to which they were randomised. The primary and secondary analyses were based on the intention-to-treat (ITT) population, defined as all randomised patients.

PRO-evaluable population included all randomised patients who had a baseline and at least 1 post-baseline assessment. PRO-evaluable population was used for descriptive analyses of visit summary, change from baseline, and mixed-effects model repeated measures (MMRM) modelling.

All safety analyses were based on the safety population, defined as all patients who receive at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil). Patients were analysed according to the treatment group as actually treated (i.e., patients who received at least one dose of venetoclax will be analysed under the VenG arm). In the event that only chlorambucil was received, the patient was analysed under the GClb arm. In the event that only obinutuzumab was received, the patient was analysed under the arm to which they were randomised.

In total, 47 patients (21.8%) in the VenG arm and 54 patients (25.0%) in the GClb arm had discontinued at least one treatment component. A full CONSORT diagram of the study population flow is provided in Appendix D.

The statistical analyses used for the primary endpoint, alongside the sample size calculations are presented in Table 11.

Table 11: Summary of statistical analyses in CLL14

Hypothesis objective	The primary objective was to test the following null and alternative hypotheses: • Null hypothesis (H_0): $PFS_{(VenG)} = PFS_{(GClb)}$ i.e. there is no difference between the two treatment arms • Alternative hypothesis (H_1): $PFS_{(VenG)} \neq PFS_{(GClb)}$ i.e. there is a difference between the two treatment arms
Statistical analysis	The primary efficacy endpoint was the investigator-assessed PFS, defined as the time from randomisation to the first occurrence of progression or relapse (determined using standard iwCLL guidelines[76]), or death from any cause, whichever occurred first. Treatment comparisons were made using a two-sided log-rank test (at 0.05 significance-level), stratified by Binet stage and geographic region. If the null hypothesis was rejected and the observed HR was favourable for the VenG experimental arm, then it was to be concluded that VenG significantly lowered the risk of PFS events more than GClb. Median PFS and the 95% confidence limits were estimated using Brookmeyer-Crowley method,[77] with the Kaplan–Meier survival curve presented to provide a visual description. PFS rates for 1, 2, and 3 years after randomisation with 95% CIs using Brookmeyer Crowley method were reported. Estimates of the treatment effect were expressed as HR including 95% confidence limits estimated through a Cox proportional-hazards analysis stratified by Binet stage and geographic region.
Sample size, power calculation	The sample size for the study was determined given the requirements to perform a hypothesis test for clinically relevant statistical superiority in the primary endpoint of PFS. Estimates of the number of events required to demonstrate efficacy with regard to PFS were based on the following assumptions: • Log-rank test at the two-sided 0.05 level of significance • Median PFS for GClb control arm (27 months) • 80% power to detect HR=0.65 for the comparison of VenG experimental arm versus GClb, with median PFS for VenG increased to 41.5 months • Exponential distribution of PFS • Annual drop-out rate of 10% • One interim analysis for efficacy after 75% of PFS events, utilising a stopping boundary according to the γ family error spending function with parameter γ=9.21 Based on these assumptions, a total of 170 PFS events were required for the final analysis of PFS. The minimum detectable difference at the final analysis corresponded approximately to an HR=0.74.

	The addition of an early interim analysis (performed after 110 events [65% of PFS events]) required no adjustment to the sample size, as the impact on the statistical power calculation was negligible. This interim analysis crossed the pre-specified boundary for the primary endpoint of α=0.0019 and so is considered the primary analysis. The PFS final analysis was designed to occur after approximately 170 IRC-assessed PFS events had occurred but as the interim analysis crossed the pre-specified boundary, the subsequent final PFS analysis was not conducted. The OS final analysis will occur at the end of the study.
Data management, patient withdrawals	All patients, including patients who discontinued all components of study therapy prior to disease progression (e.g., for toxicity), continued in the study and were in follow-up for progressive disease and survival regardless of whether or not they subsequently received new anti-leukemic therapy.

Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; IRC: independent review committee; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70]

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Overall, the results of the CLL14 trial may be considered to be at low risk of bias. Randomisation and concealment of treatment allocation was adequate. Baseline characteristics were well-balanced between the treatment groups at baseline. All randomised patients were included in the ITT analysis for primary and secondary efficacy outcomes.

Table 12: Overview of quality assessment for CLL14

	Response	Justification
Was randomisation carried out appropriately?	Yes	Randomisation was performed by an interactive voice-/web-based system. Patients were assigned in 1:1 ratio to one of the two treatment groups through a block stratified randomisation procedure according to the Binet stage (3 levels – A, B or C) and geographic region.
Was the concealment of treatment allocation adequate?	Yes	Randomisation was computer generated and assignment made by a web and voice mail-based system
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	The characteristics of the patients were well balanced between the two groups, hence there were no significant differences.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	The study was open-label in design due to the differences in treatment schedules: venetoclax is initiated on Cycle 1 Day 22 and administered daily, whereas chlorambucil is initiated on Cycle 1 Day 1 and administered on Day 1 and 15 at each cycle. Neither the subjects nor the investigators were blinded to treatment. The IRC was blinded throughout the study to treatment assignment and

		relevant clinical data such as response and progression/non-progression.
Were there any unexpected imbalances in drop-outs between groups?	No	Two patients in the GClb arm and four patients in the VenG arm did not receive full trial treatments but were included in the efficacy analyses since they met the criteria for inclusion in the ITT population: • In the GClb arm 1 patient died and 1 patient withdrew from the study prior to dosing • In the VenG arm 4 patients withdrew from the study prior to dosing Sensitivity analysis of the primary endpoint was conducted for PFS by investigator and IRC assessments.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes presented in the methods of the CLL14 publications were subsequently reported in the results
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	An ITT population was used for analysis of all efficacy endpoints. Appropriate measures were taken to account for missing data.

Abbreviations: GClb: chlorambucil with obinutuzumab; IRC: independent review committee; ITT: intention-to-treat population; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

B.2.6 *Clinical effectiveness results of the relevant trials*

B.2.6.1 Overview of results

The following section of this submission presents the results of the August 2018 data cut from the CLL14 trial (median 28.1 months follow-up), at which time all patients had completed 12 cycles of treatment.

The primary endpoint of the trial was investigator-assessed PFS and is validated by independent review committee (IRC) PFS results (this outcome is utilised in the cost-effectiveness model presented in Section B.3). Secondary endpoints that are utilised in the economic model include adverse effects of treatment and health-related quality of life (HRQoL). All secondary endpoints presented below are investigator assessed.

Overall survival (OS) results are presented here but are not used in the economic model as the data are not statistically significant and too immature to be meaningful (<10% of enrolled patients had died), due to the first-line position of treatment and the natural history of CLL.

B.2.6.2 Progression-free survival (PFS)

PFS by investigator assessment (primary endpoint)

At the time of clinical cut-off, all patients had been off-treatment for a median of 17.1 months (range: 0.0–30.4) in the VenG arm and 17.9 months (0.0–30.2) in the GClb arm. After a median follow-up of 28.1 months (0.0–35.9), the investigator assessed PFS was significantly higher in

patients in the VenG arm (30 events in 216 patients including 14 with progressive disease [PD] and 16 deaths) than in patients in the GClb arm (77 events in 216 patients including 69 PDs and 8 deaths) with hazard ratio (HR) = 0.35; 95% CI: 0.23, 0.53; p<0.001 (stratified log-rank test). The number of patients with PFS events on or after treatment is very low in the VenG arm (13.9%) when compared to the GClb arm (35.6%) (Table 13).

Table 13: Investigator-assessed PFS results

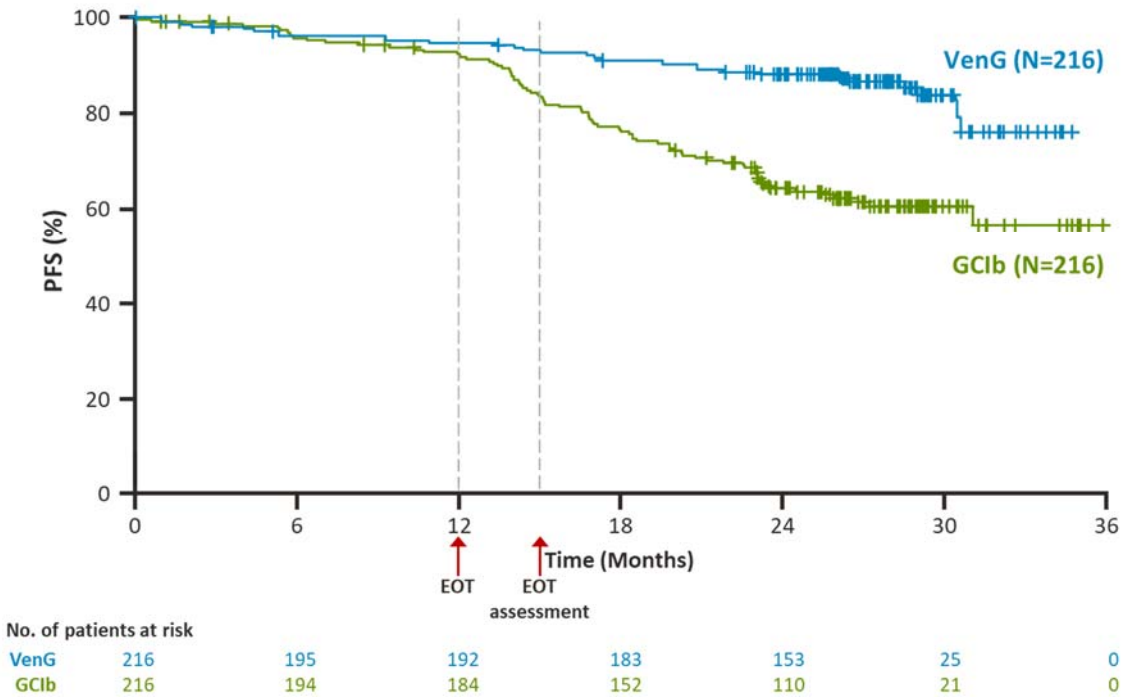
	Events, n (%)	HR (95% CI)	Stratified p value	Pre-specified IA boundary	PFS 1 Year (%)	PFS 2 Year (%)
VenG (N=216)	30* (13.9)	0.35 (0.23, 0.53)	<0.001	p=0.0009	[redacted]	88.2
GClb (N=216)	77† (35.6)				[redacted]	64.1

*14 PD and 16 deaths; †69 PD and 8 deaths
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; IA: interim analysis; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

Investigator-assessed PFS results are presented in Table 13. Median PFS was not reached in either study arm, however the improvement seen in PFS was statistically significant and clinically meaningful. A high proportion of patients in the VenG treatment arm remained progression free after 24 months.

The Kaplan–Meier plots show separation of the curves in favour of VenG after 6 months, which was maintained over time, based on 28.1 months follow-up (Figure 3).

Figure 3: Kaplan–Meier plot of investigator-assessed PFS



Abbreviations: EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up).

PFS by Independent Review Committee (IRC) assessment (secondary endpoint)

At the time of clinical cut-off, the IRC-assessed PFS was consistent with the investigator-assessed PFS showing reduced risk of having a PFS event (defined as disease progression or death) for patients in the VenG arm. Similar to the investigator-assessed PFS results, the IRC-assessed PFS was significantly higher in the VenG arm (29 events in 216 patients including [redacted] PDs and [redacted] deaths) than in patients in the GClb arm (79 events in 216 patients including [redacted] PDs and [redacted] deaths) with stratified HR 0.33; 95% CI: 0.22, 0.51; p<0.0001, stratified log-rank test. The median PFS had not been reached in either treatment arm.

Table 14: IRC-assessed PFS results

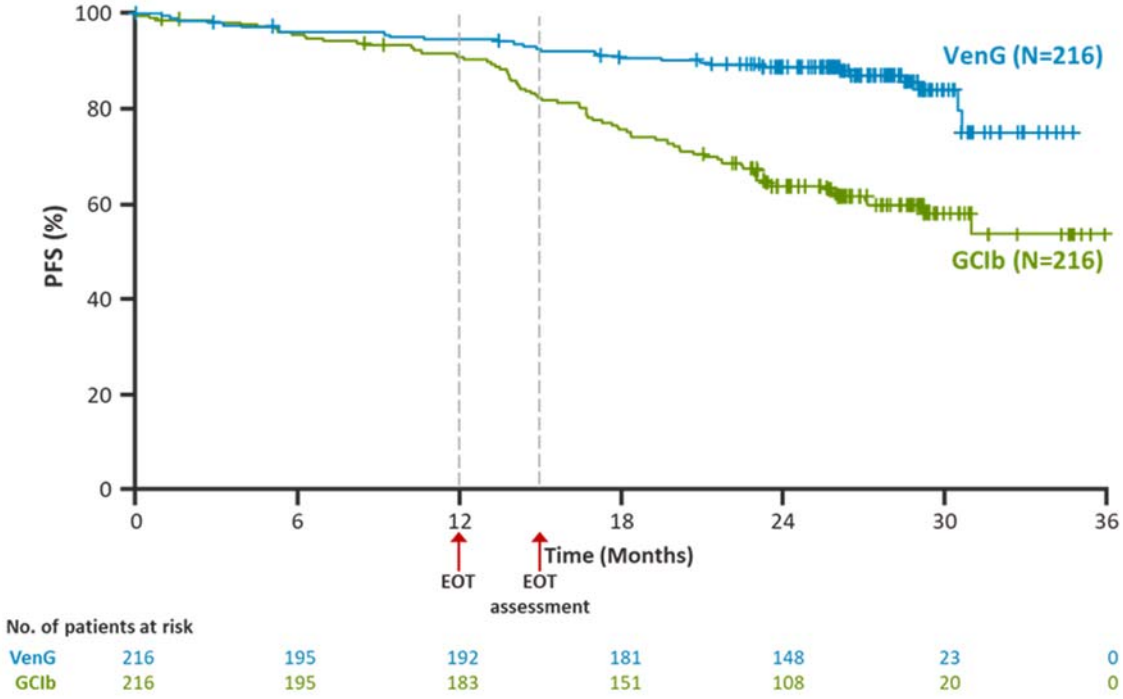
	Events, n (%)	HR (95% CI)	Stratified p value	PFS 1 Year (%)	PFS 2 Year (%)
VenG (N=216)	29* (13.4)	0.33 (0.22, 0.51)	<0.0001	[redacted]	88.6
GClb (N=216)	79† (36.6)			[redacted]	63.7

*[redacted] PD and [redacted] deaths(the IRC considered [redacted] patient recorded by the investigator as a death had experienced a PD event prior to death); †[redacted] PD and [redacted] deaths
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

Progression-free estimates at 12 and 24 months are presented in Table 14, demonstrating a high proportion of patients who remained progression free over 28.1 months of follow-up in the VenG arm.

The Kaplan–Meier plots (IRC-assessed) show separation of the curves in favour of VenG after 6 months, which was maintained over time (Figure 4).

Figure 4: Kaplan–Meier plot of IRC-assessed PFS



[redacted]concordance between IRC and investigator assessments
Abbreviations: EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; IRC: independent review committee; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up).

Concordance between the investigator assessed and IRC assessed PFS was analysed in terms of whether there was an event and the type of event (PD or death). The results between the two analysis methods were highly consistent; concordance between the IRC-assessed and the investigator assessed PFS events and censor status (i.e., agreement on PD, death, or no PD event) was high ([redacted]%, Table 15), and the timing of PD or no PD event was also consistent between investigator assessments and IRC assessments (stratified HR ranged from 0.33–0.35).

Table 15: Overall concordance analysis between IRC-determined and investigator-determined PD status

Investigator assessment	IRC assessment	VenG (N=216)	GClb (N=216)
PD event	PD event	[redacted]	[redacted]
	Death	[redacted]	[redacted]
	No event	[redacted]	[redacted]
Death	PD event	[redacted]	[redacted]
	Death	[redacted]	[redacted]
	No event	[redacted]	[redacted]
No event	PD event	[redacted]	[redacted]
	Death	[redacted]	[redacted]
	No event	[redacted]	[redacted]

Abbreviations: GClb: chlorambucil with obinutuzumab; IRC: independent review committee; PD: progressive disease; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

Benefits in PFS were also maintained across major clinical and biologic subgroups including patients with del(17p)/*TP53* mutation as well as without del(17p)/*TP53* mutation (Section B.2.7). These results demonstrate that VenG provides a statistically significant and clinically meaningful improvement in PFS, making VenG an important addition to the currently limited range of available treatment options in previously untreated CLL.

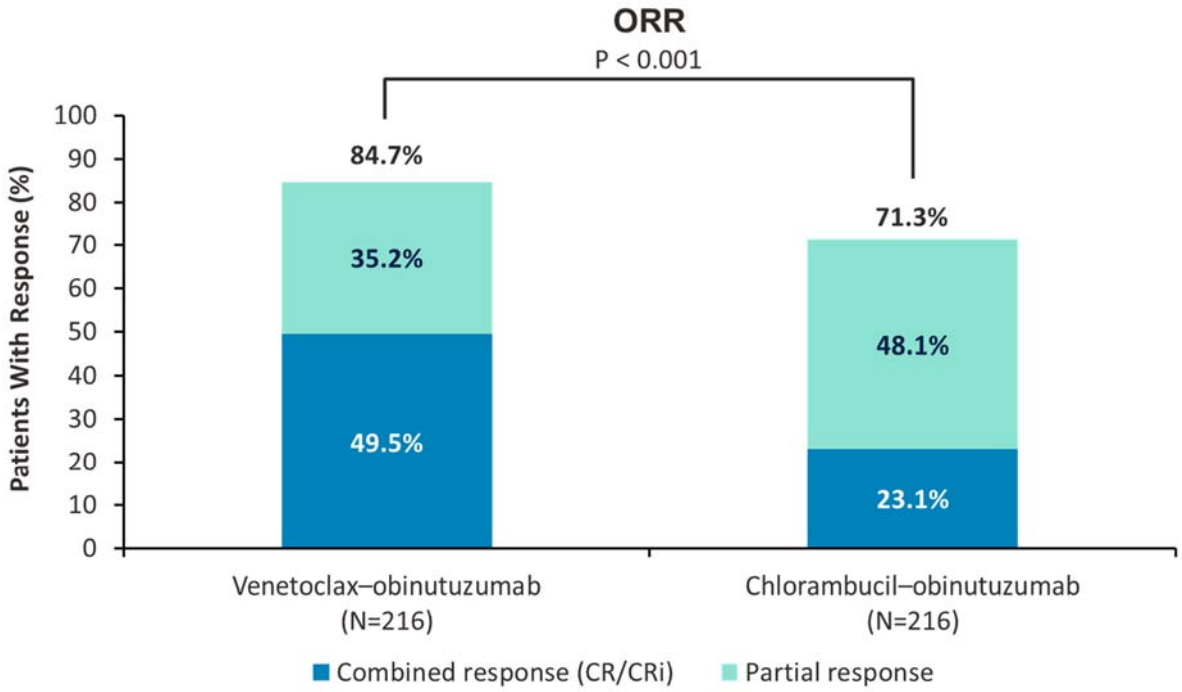
B.2.6.3 Response rates

Overall response rate (ORR)

ORR was defined as rate of a clinical response of complete response (CR), complete response with incomplete bone marrow recovery (CRi) or partial response (PR) at the completion of treatment assessment (end of treatment [EOT] assessment i.e., 3 months after treatment completion/early termination), as determined by the investigator according to the iwCLL guidelines.[76]

At EOT assessment, there was a statistically significant difference in the proportion of patients achieving ORR per investigator assessment in favour of the VenG arm compared with the GClb arm (difference 13.4% [95% CI: [redacted]]; Figure 5).

Figure 5: ORR at EOT assessment



Abbreviations: CR: complete response; CRi: complete response with incomplete bone marrow recovery; EOT: end-of-treatment; ORR: overall response rate.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up).

Combined response

A combined response of CR or CRi at the completion of treatment assessment (EOT assessment i.e. 3 months after treatment completion/early termination), was determined by the investigator according to the iwCLL guidelines.[76]

Table 16 presents the proportion of patients in both treatment arms who achieved CR or CRi, and the proportion who were therefore considered non-responders to treatment. A clinically meaningful difference was observed in the rate of patients achieving CR/CRi, with patients in the VenG treatment arm achieving a higher rate of CR/CRi compared with patients in the GClb arm.

Table 16: CRR at EOT assessment

	VenG (N=216)	GClb (N=216)
CR – n (%)	[redacted]	[redacted]
CRi – n (%)	[redacted]	[redacted]
Combined response (CR+CRi) – n (%)	107 (49.5)	50 (23.1)
Non-responders – n (%)	109 (50.5)	166 (76.9)
95% CI for Response Rates	[redacted]	[redacted]
Difference in Complete Response Rate (95% CI)	26.4 (17.4, 35.4)	
p value	<0.0001	
Odds Ratio (95% CI)	3.3 (2.2, 5.1)	

Abbreviations: CI: confidence interval; CR: complete response; CRi: complete response with incomplete bone marrow recovery; CRR: complete response rate; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

B.2.6.4 Minimal residual disease (MRD)

Minimal residual disease at EOT and over time

Minimal residual disease (MRD) was assessed by ASO-PCR assay and confirmed by flow cytometry, in accordance with international guidelines.[35, 78, 79] MRD was measured in both peripheral-blood (at baseline, cycles 7, 9 and 12, and then every 3 months thereafter) and in the bone marrow of patients with treatment response (at cycle 9 and 3 months after treatment completion), with a threshold for undetectable MRD of 10^{-4} [i.e. <1 cell in 10,000 leukocytes].[1]

At EOT (three months after treatment completion), a higher proportion of patients in the VenG arm versus GClb arm had undetectable MRD in the peripheral blood (163 of 216 patients [75.5%] vs 76 of 216 patients [35.2%], p<0.001, Table 17), and the same was also true for undetectable MRD in bone marrow (123 of 216 patients [56.9%] vs 37 of 216 patients [17.1%], p<0.001, Table 17).[1]

Table 17: Undetectable MRD rates at EOT

	Undetectable MRD, n (%)*	Detectable MRD, n (%)**	Difference in undetectable MRD rates (95% CI)	p value	OR (95% CI)
Peripheral Blood					
VenG	163 (75.5)	53 (24.5)	40.3 (31.5, 49.1)	<0.001	5.7 (3.7, 8.6)
GClb	76 (35.2)	140 (64.8)			

Bone Marrow					
VenG	123 (56.9)	93 (43.1)	39.8 (31.3, 48.4)	<0.001	6.4 (4.1, 10.0)
GClb	37 (17.1)	179 (82.9)			

*Undetectable MRD $<10^{-4}$
**Includes MRD missing and non-evaluable samples
Abbreviations: CI: confidence interval; EOT: end-of-treatment; GClb; chlorambucil with obinutuzumab; MRD: minimal residual disease; OR: odds ratio; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70]

In the peripheral blood, the difference in undetectable MRD between the VenG arm and the GClb arm was observed as early as Cycle 7 Day 1, with [redacted] ([redacted] and [redacted] ([redacted] patients achieving undetectable MRD in the VenG and GClb arms, respectively (difference: [redacted] [95% CI: [redacted]] in favour of the VenG arm). The higher rate of undetectable MRD in the VenG arm was sustained throughout the treatment period, and during follow-up off-treatment (August 2018 data cut: 28.1 months median follow-up). One year after treatment cessation the proportion of patients with undetectable MRD in the peripheral blood was maintained at [redacted] in the VenG arm but had dropped to [redacted] in the GClb arm (difference: [redacted] [95% CI: [redacted]]). Undetectable MRD rates in peripheral blood over time are presented in Figure 6. Undetectable MRD rates in bone marrow were also consistently higher in the VenG arm over the follow-up period.[70]

Figure 6: Undetectable MRD in peripheral blood over time

Abbreviations: C7D1: Cycle 7, Day 1; C9D1: Cycle 9, Day 1; C12D1: Cycle 12, Day 1; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PD: progressive disease; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (Undetectable MRD results)[80]

Concordance between MRD in peripheral blood and bone marrow

There was a general high concordance of MRD status between paired peripheral blood and bone marrow samples at EOT in both the GClb arm ([redacted]%) and VenG arm ([redacted]%) based on ASO-PCR analysis.

The strong concordance between MRD status in blood and bone marrow in matched samples suggests that the undetectable MRD rates in blood were comparable with undetectable MRD

rates in bone marrow. Therefore, undetectable MRD in peripheral blood is a clear indication of undetectable MRD in VenG treated patients. The higher concordance of having undetectable MRD between peripheral blood and bone marrow in paired EOT assessment samples observed in the VenG arm ([redacted]%) compared with the GClb arm ([redacted]%) suggests VenG could more effectively clear MRD in both peripheral blood and bone marrow compartments due to its deep MRD response.

Minimal residual disease and clinical response outcomes

Amongst investigator assessed complete responders at EOT, patients in the VenG arm achieved statistically significantly higher bone marrow undetectable MRD rates (33.8%) when compared to patients in the GClb arm (10.6%). The same result was seen when MRD was assessed in the peripheral blood, with the proportion of complete responders achieving undetectable MRD in the VenG and GClb arms of 42.1% and 14.4% respectively (p<0.0001).

Table 18: Undetectable MRD rates in patients with CR at EOT

	Undetectable MRD, n (%)*	Detectable MRD, n (%)**	Difference in undetectable MRD rates (95% CI)	p value	OR (95% CI)
Peripheral Blood					
VenG	94 (42.1)	125 (57.9)	27.8 (19.5, 36.1)	<0.0001	4.3 (2.7, 6.9)
GClb	31 (14.4)	185 (85.6)			
Bone Marrow					
VenG	73 (33.8)	143 (66.2)	23.2 (15.4, 30.9)	<0.0001	4.3 (2.6, 7.2)
GClb	23 (10.6)	193 (89.4)			

*CR status as assessed by investigator, undetectable MRD $<10^{-4}$
**Includes MRD missing and non-evaluable samples
Abbreviations: CI: confidence interval; CR: complete response; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; OR: odds ratio; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

Minimal residual disease and PFS

Landmark analysis was conducted across the two treatment arms based on EOT assessment of both peripheral blood (Figure 7) and bone marrow (Figure 8).

MRD status and results demonstrated that CLL14 patients achieving undetectable MRD in either peripheral blood or bone marrow assessment had a longer PFS compared with patients who had detectable MRD at EOT. This result highlights the importance of patients achieving undetectable MRD to experience a durable response to treatment.

Figure 7: Kaplan–Meier plot of investigator assessed PFS status based on MRD status in the peripheral blood at EOT assessment

Abbreviations: EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)

Figure 8: Kaplan–Meier plot of investigator assessed PFS status based on MRD status in the bone marrow at EOT assessment

Abbreviations: EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)

B.2.6.5 Overall survival (OS)

OS, the time between the date of randomisation and the date of death due to any cause, was assessed as a secondary endpoint.

At data cut-off (August 2018: 28.1 months median follow-up), a total of 37 randomised patients had died; 20 patients (9.3%) in the VenG arm and 17 patients (7.9%) in the GClb arm (1 patient died prior to receiving any treatment). The median OS was not reached in either arm and there was no evidence of difference in OS between the two arms. CLL14 OS results are presented in Table 19 and the corresponding Kaplan–Meier plot is provided in Figure 9.

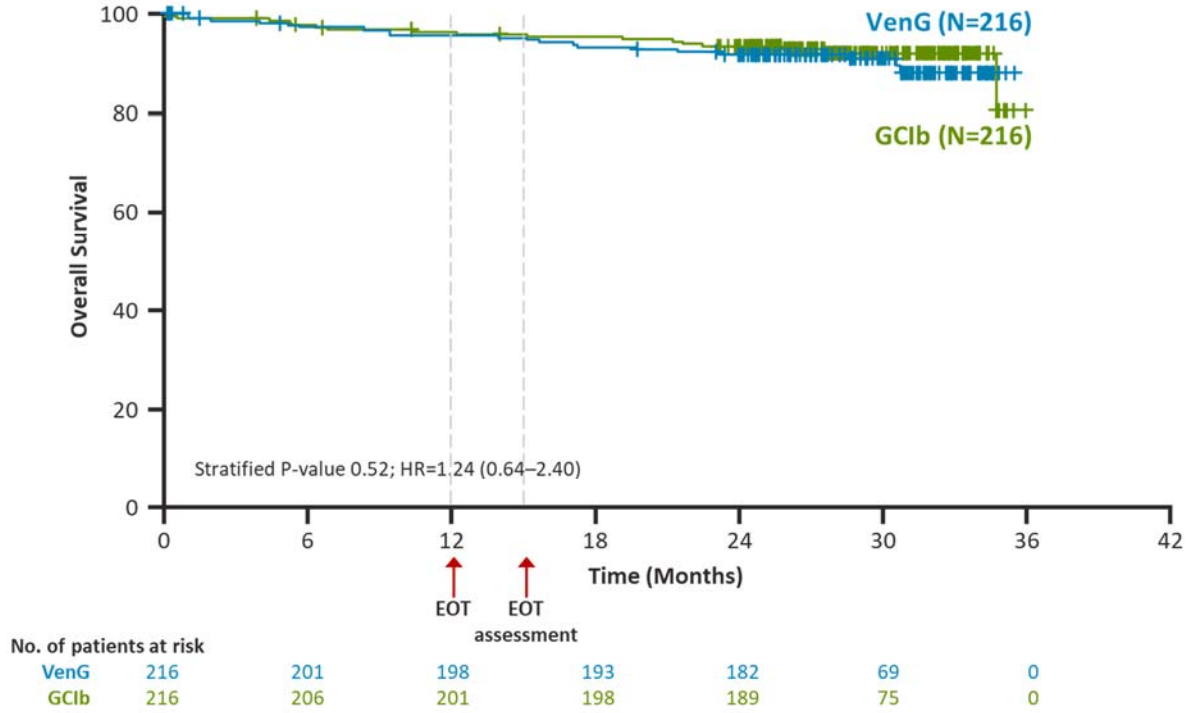
The OS data are too immature to be meaningful (<10% of enrolled patients had died), due to the first-line position of treatment – where results are confounded by the availability of treatments for relapsed/refractory CLL – and the natural history of CLL, and therefore are not interpretable at this time.

Table 19: OS results (interim analysis)

	Events n (%)	HR (95% CI)	Stratified p value	Pre-specified IA boundary	OS 1 Year (%)	OS 2 Year (%)
VenG (N=216)	20 (9.3)	1.24 (0.64, 2.40)	0.52	p=0.007	[redacted]	91.8
GClb (N=216)	17 (7.9)				[redacted]	93.3

Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; IA: interim analysis; HR: hazard ratio; OS: overall survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

Figure 9: Kaplan–Meier plot of OS



Abbreviations: GClb: chlorambucil with obinutuzumab; HR: hazard ratio; OS: overall survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up).

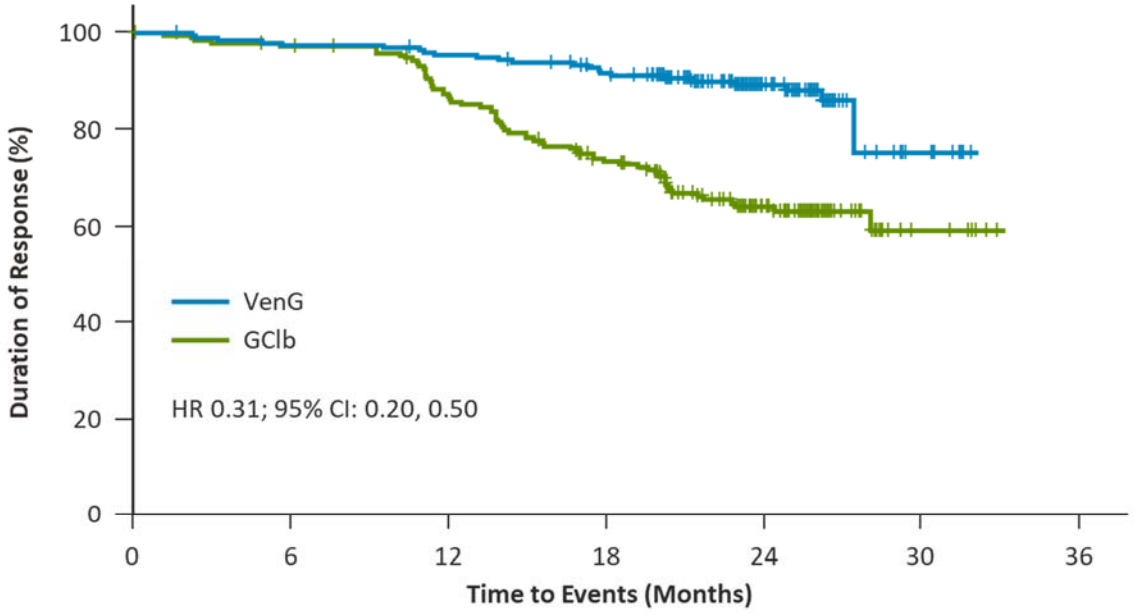
B.2.6.6 Duration of response

The duration of response was calculated only for the patients who responded per definition, 197 in GClb and 200 in VenG.

Duration of response was prolonged in the VenG arm compared with the GClb arm (stratified: HR 0.31, 95% CI: 0.20, 0.50; p[redacted] and unstratified: HR [redacted], 95% CI: [redacted] p[redacted]). The event free rates (where event referred to disease progression as assessed by the investigator or death) at 24 months were [redacted] in VenG arm compared with [redacted] in GClb arm. However, the median duration of response was not reached in either treatment arm.

The Kaplan–Meier plots showed separation of the curves in favour of VenG around 9 months, which was maintained over time (Figure 10).

Figure 10: Kaplan–Meier plot of duration of response



Number of patients at risk

VenG	200	191	186	173	86	8	0
GClb	197	187	163	131	66	7	0

Abbreviations: CI: confidence interval; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up).

B.2.6.7 Event-free survival (EFS)

At clinical cut-off, the median EFS was not reached in either treatment arms. Patients treated with VenG combination show higher duration of EFS and reduced risk of having an EFS event (progression, death or start of new anti-CLL therapy) than GClb (stratified: HR 0.36, 95% CI: 0.24, 0.54; [redacted] and unstratified: HR [redacted], 95% CI: [redacted]; [redacted]) (Table 20).

Table 20: Summary of event-free survival results

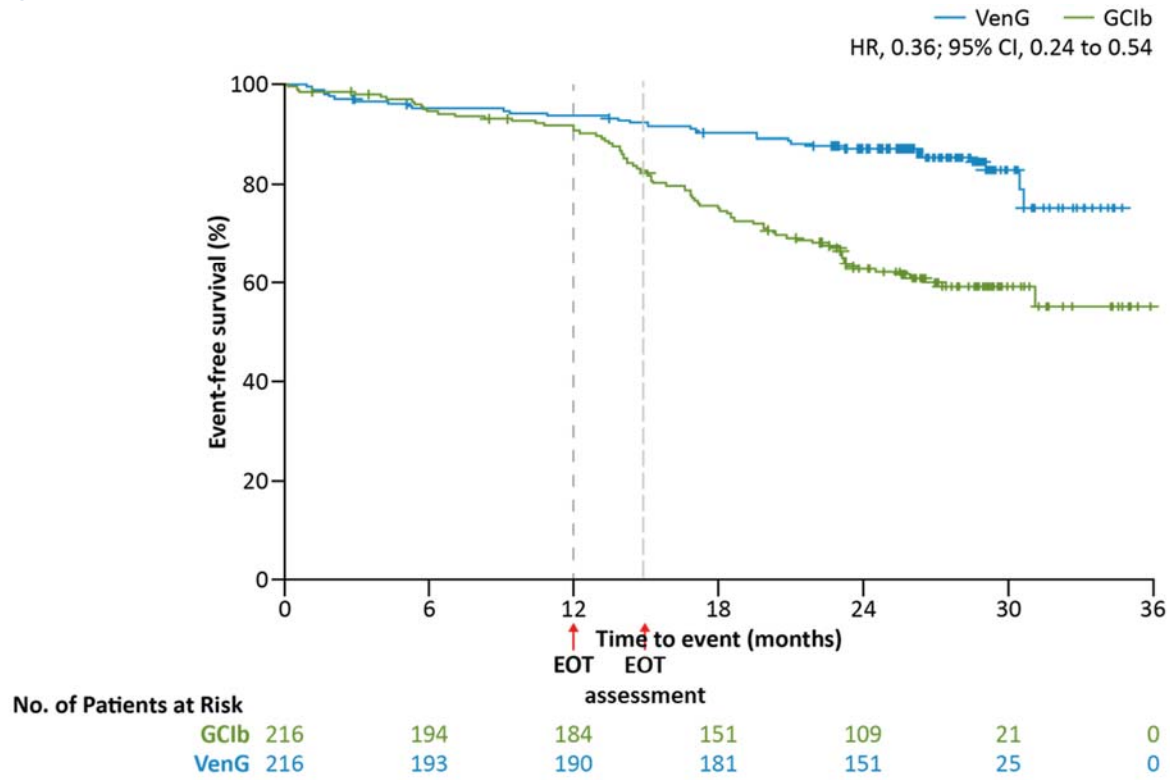
	Patients with event, n (%)	Earliest contributing event, n			HR (95% CI)	Stratified p value
		New anti-leukemic treatment	Disease progression	Death		
VenG (N=216)	[redacted]	[redacted]	[redacted]	[redacted]	0.36 (0.24, 0.54)	[redacted]
GClb (N=216)	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

Over time, the VenG arm showed higher rates of EFS than GClb – the event free rate at 12 months was [redacted]% in the VenG arm and [redacted]% in GClb arm, and at 24 months the rate was [redacted]% in the VenG arm and [redacted]% in the GClb arm.

The corresponding Kaplan–Meier plot is provided in Figure 11.

Figure 11: Kaplan–Meier plot for EFS



Abbreviations: CI: confidence interval; EFS: event-free survival; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up).

B.2.6.8 Time-to-next treatment (TTNT)

Time to new anti-CLL treatment is defined as time between the date of randomisation and the date of first intake of new anti-leukemic therapy. The disease progression could result in discontinuation, or death before the first intake of new anti-leukemic therapy.

At the cut-off date, [redacted]patients in the GClb arm and [redacted]patients in the VenG arm had started a new anti-leukemic therapy. The risk of starting a new treatment was reduced in the VenG arm compared with patients in the GClb arm (stratified: HR 0.60; 95% CI: 0.37, 0.97; p=[redacted]and unstratified: HR [redacted]; 95% CI: [redacted]; p=[redacted]) (Table 21).

Table 21: Summary of time-to-next treatment results

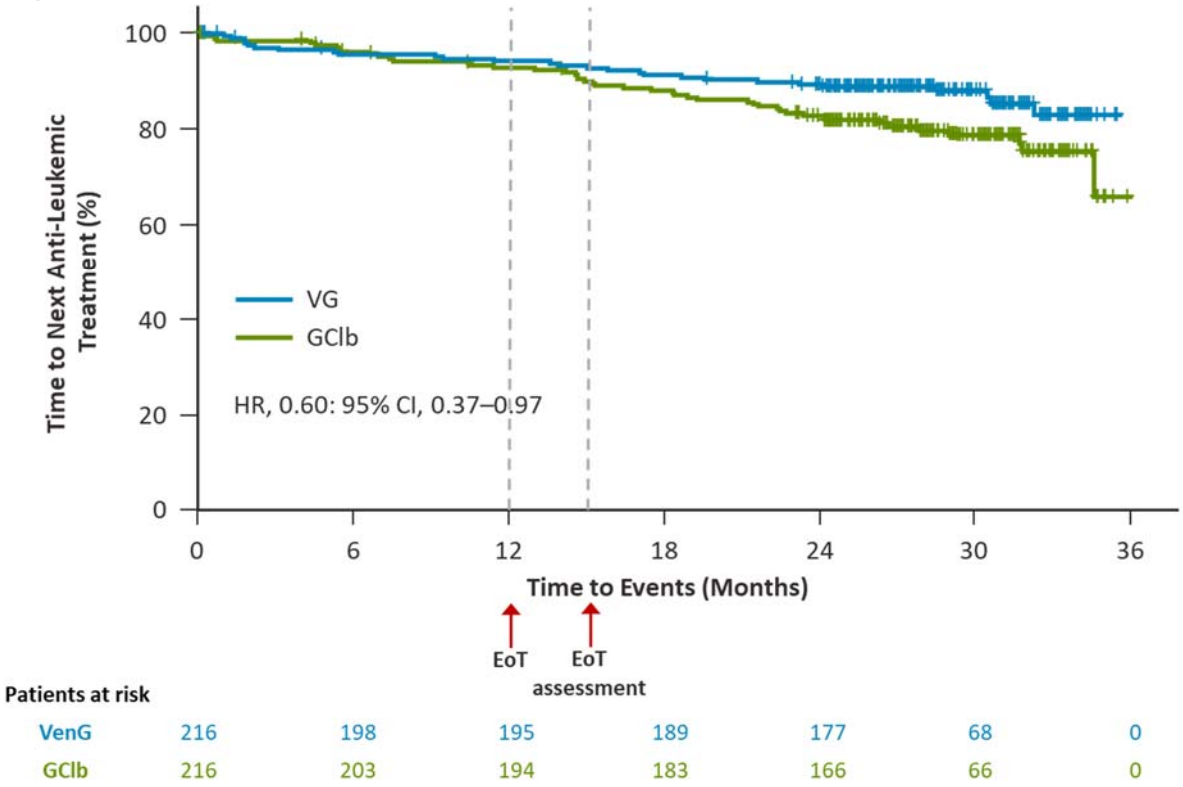
	Patients with event, n (%)	Earliest contributing event, n		HR (95% CI)	Stratified p value
		New anti-leukemic treatment	Death*		
VenG (N=216)	[redacted]	[redacted]	[redacted]	0.60 (0.37, 0.97)	[redacted]
GClb (N=216)	[redacted]	[redacted]	[redacted]		

*Note that the number of deaths recorded in this analysis is lower than the total for the data cut because some patients had begun a new anti-leukemic treatment prior to death, and it is the earliest event that counts here
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70] (August 2018 data cut: 28.1 months follow-up).

The median time to new anti-CLL treatment was not reached in either treatment arms. The difference in time to next anti-leukemic treatment between the VenG arm and GClb became more evident over time – the time point analysis at 12 months was [redacted] in the VenG arm and [redacted] in GClb arm, and [redacted] in the VenG arm and [redacted] in the GClb arm at 24 months.

The Kaplan–Meier plots showed separation of the curves in favour of VenG around 15 months, which was maintained over time (Figure 12).

Figure 12: Kaplan–Meier plot for TTNT



Abbreviations: CI: confidence interval; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1] (August 2018 data cut: 28.1 months follow-up

B.2.6.9 Patient reported outcomes (PROs)

Patients followed the same schedule of PRO assessments during treatment and follow-up regardless of treatment arm.

PRO completion over the course of the trial was very high. The proportion of patients completing at least one item of the MD Anderson Symptom Inventory (MDASI), EORTC QLQ-C30, and EQ-5D-3L was [redacted] at baseline and [redacted] in both arms during treatment. Completion rates dropped slightly during follow-up but remained [redacted] in both arms until Month 30. No notable differences in compliance over the course of the trial were observed between the two arms.

As the most relevant measure of HRQoL for the economic model, the results for EQ-5D-3L are presented here, with results for MDASI and EORTC QCQ-C30 presented in Appendix L.

EQ-5D-3L

Mean health utility was high on average at baseline and comparable between the two arms. Mean scores remained stable throughout treatment and follow-up. Mean visual analogue scale (VAS) scores were moderate at baseline and comparable between the two arms. Patients experienced clinically meaningful improvement in mean scores (≥7 points) in the VenG arm starting at cycle 2 and the GClb arm starting at cycle 6. Improvement continued throughout the remainder of treatment and follow-up.[81]

The proportion of patients experiencing no problems across the five health states was moderate-to-high at baseline and comparable between the VenG and GClb arms. The proportion of responses was largely stable across treatment and follow-up with the vast majority of patients reporting “no problems” and very few patients reporting severe limitations (≤8 patients at any time-point). Patients in both arms reported a slight improvement in usual activities and anxiety/depression during treatment but only the latter was maintained post-treatment.

The mean change in baseline scores for each category are presented graphically in Figure 13 and Figure 14. Notably, when considered with the efficacy data presented above, VenG provided a much deeper response and superior PFS without resulting in a reduction in HRQoL.

Figure 13: Change from baseline in EQ-5D-3L for utility 1–5 score

Utility: Questions 1 to 5 combined, transformed to utility values (5 items)
Abbreviations: EQ-5D-3L: European Quality of Life 5 dimensions 3 level version; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)[70]

Figure 14: Change from baseline in EQ-5D-3L for 'your own health today' score

VAS: Question 6 (1 item)
Abbreviations: EQ-5D-3L: European Quality of Life 5 dimensions 3 level version; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)[70]

B.2.7 *Subgroup analysis*

The VenG arm of the CLL14 trial showed consistent treatment effects across major clinical and biologic subgroups, including high-risk patients such as those with del(17p)/*TP53* mutation, which were also consistent with the primary analysis.

Pre-specified subgroup analyses of the primary endpoint of investigator-assessed PFS were performed to evaluate internal consistency of the primary efficacy analysis and to determine whether baseline clinical characteristics or molecular features had an impact on the efficacy of VenG compared with GClb. The different subgroups considered are presented in Table 22.

Table 22: Pre-planned subgroups for PFS

Variable	Comparison
Age	<75 years vs ≥75 years
Gender	Male vs female
Binet stage at screening	A, B, C
Cytogenetic subgroups	Del(17p), del(11q), trisomy 12, no abnormalities, del(13q)
TP53 deletion and/or mutation	Present vs not present

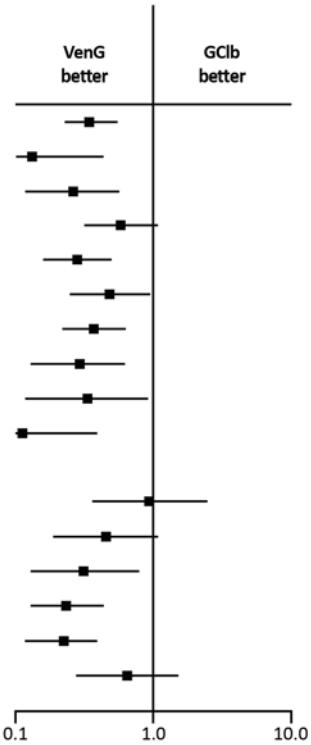
Abbreviations: del(11q): chromosome 11q deletion; del(13q): chromosome 13q deletion; del(17p): chromosome 17p deletion; PFS: progression-free survival.
Source: Fischer et al. 2019[1]

Overall, the data provided evidence of consistent improvements in both investigator-assessed PFS and IRC-assessed PFS in patients treated with VenG in major clinical and biologic

subgroups including high-risk and low-risk as well as young and older patients. A summary forest plot of the investigator-assessed PFS subgroup analyses for the subgroups described in Table 22 is presented in Figure 15.

Figure 15: Investigator-assessed PFS by prognostic subgroup

			GClb			VenG				
Category	Subgroup	Total n	n	Events	PFS rate month 24 (%)	n	Events	PFS rate month 24 (%)	Hazard ratio	95% Wald CI
All		432	216	77	64.1	216	30	88.1	0.34	0.23–0.53
Binet stage at screening	A	90	44	18	56.6	46	3	95.7	0.13	0.04–0.42
	B	157	80	30	62.5	77	9	88.9	0.26	0.12–0.55
	C	185	92	29	69.1	93	18	83.4	0.58	0.32–1.05
Age groups (years)	<75	282	138	49	63.5	144	17	89.7	0.28	0.16–0.48
	≥75	150	78	28	65.1	72	13	84.9	0.48	0.25–0.93
Gender	Male	289	143	49	65.4	146	21	87.7	0.37	0.22–0.61
	Female	143	73	28	61.4	70	9	89.1	0.29	0.13–0.60
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	10	23.1	17	7	64.7	0.33	0.12–0.89
	del(11q)	74	38	20	41.3	36	4	91.2	0.11	0.03–0.38
	Trisomy 12	76	40	17	55.6	36	0	100.0	NE	NE
	No abnormalities	92	42	8	82.1	50	9	87.2	0.93	0.36–2.41
	del(13q)	120	59	16	78.3	61	8	88.1	0.45	0.19–1.05
TP53 deletion and/or mutation	Present	46	22	15	32.7	24	7	73.9	0.31	0.13–0.76
	Not present	287	139	49	65.0	148	14	92.1	0.23	0.13–0.42
IGHV mutational status	Unmutated	244	123	57	51.0	121	16	89.4	0.22	0.12–0.38
	Mutated	159	83	15	85.6	76	9	90.3	0.64	0.28–1.46



Abbreviations: CI: confidence interval; del(11q): chromosome 11q deletion; del(13q): chromosome 13q deletion; del(17p): chromosome 17p deletion; GClb: chlorambucil with obinutuzumab; *IGHV*: immunoglobulin heavy-chain variable region; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1]

Cytogenetic subgroups

Patients with a del(17p)/*TP53* mutation have been observed to have significantly inferior disease response, duration of response and OS on standard CLL treatments.[15, 16] As such, they are considered as high-risk patients with a significant unmet need for new treatment options.

For patients with del(17p), the primary outcome of investigator-assessed PFS for VenG compared with GClb was consistent with that of the overall trial population (HR 0.33; 95% CI: 0.12, 0.89 compared with HR 0.34; 95% CI: 0.23, 0.53). The same was also observed for patients with *TP53* deletion and/or mutation (HR 0.31; 95% CI: 0.13, 0.76).

These results demonstrate that VenG has been shown to consistently outperform GClb, even within high-risk patient subgroups, providing clinically meaningful improvements in PFS in all populations, including those with few treatment options currently available to them.

B.2.8 *Meta-analysis*

Due to the identification of only one study evaluating the efficacy and safety of venetoclax with obinutuzumab in patients with previously untreated CLL (see Section B.2.9.1), no meta-analysis was performed.

Individual patient data (IPD) from the CLL14 trial were used as the best available evidence for direct comparison to GClb. For the comparison to ibrutinib in the del(17p)/*TP53* mutation population, please see Section B.2.9.1.

B.2.9 *Indirect and mixed treatment comparisons*

For the population of patients with del(17p)/*TP53* mutation, unadjusted naïve indirect comparisons to ibrutinib demonstrated no statistically significant benefits for either treatment

- An SLR identified four publications that presented data for ibrutinib in a del(17p)/*TP53* population.
- A feasibility assessment determined there was insufficient data on CLL patients receiving ibrutinib as first-line treatment to allow for a matching-adjusted indirect comparison (MAIC).
- Unadjusted HRs between ibrutinib and VenG were calculated as [redacted] for PFS (p=[redacted]; 95% CI: [redacted]), and [redacted] for OS (p=[redacted]; 95% CI: [redacted]), however none of the results were statistically significant due to the small population sizes of the studies included in the analysis.

B.2.9.1 Identification of comparator trials

An SLR was conducted to identify literature reporting clinical evidence for the efficacy, safety and tolerability of the treatment of adults with previously untreated CLL with VenG and its comparators. The details of this SLR are presented in Appendix D.

Study Selection

As described in Section B.1.3.4, there are only two directly relevant comparators for VenG in clinical practice: GClb for patients without del(17p)/*TP53* mutation and ibrutinib for patients with del(17p)/*TP53* mutation. These were determined considering NICE guidance and guidelines published by the BSH, and were validated by a panel of clinical experts at an AbbVie-organised HTA advisory board.

GClb – patients without del(17p)/TP53 mutation

The CLL14 trial provides direct comparison of efficacy and safety outcomes for VenG with GClb and is presented in Section B.2.

Ibrutinib – patients with del(17p)/TP53 mutation

Less than 10% of patients in the first-line CLL setting present with del(17p)/*TP53* mutation and therefore only a small number of these patients are recruited into clinical trials, leading to a general paucity of evidence for this population. For these reasons, there is a lack of evidence for both VenG and ibrutinib in the first-line CLL del(17p)/*TP53* population. This lack of data creates challenges for comparative evidence synthesis, particularly when limited trial data is available

directly comparing the relevant interventions in this population. Ibrutinib specifically received its recommendation from NICE for this indication despite having no data in first-line del(17p)/*TP53* mutated patients, due to the high unmet need for an available therapy in this population. Uncertainty is associated with this recommendation since no robust evidence base was presented for this population.

For the first-line population with del(17p)/*TP53* mutation, the SLR identified three studies presenting data for ibrutinib:

- A phase 2 single-arm study (Farooqui et al. 2015) with 5-year follow-up (Ahn et al. 2018)[71, 72]
- A real word evidence study (Mato et al. 2018),[60] assessing efficacy in patients excluded from the RESONATE 2 study (discussed in Section B.1.3.4) for having del(17p)/*TP53* mutation
- A phase 3 randomised trial (ALLIANCE).[73] However, fewer than 10 patients in the ALLIANCE trial had del(17p) and therefore the trial this was excluded from the indirect treatment comparison (ITC) analysis due to its small sample size

No direct head-to-head evidence exists between VenG and ibrutinib in previously untreated CLL patients with del(17p)/*TP53* mutation, meaning an ITC approach was required.

Table 23: Studies included in ITC analysis, as identified by the clinical SLR

Study	Citation	Overview of data
Farooqui (2015) Secondary publication: Ahn (2018)	Farooqui, M. Z. et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with *TP53* aberrations: a phase 2, single-arm trial. The Lancet Oncology 16, 169-176 (2015). NCT Number: NCT01500733 Follow-up data: Ahn, J. E. et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 131(21):2357–2366 (2018).	The study by Farooqui reported on a phase 2, open-label single-arm trial of ibrutinib with a data cut-off of August 1st, 2014. This study investigated the safety and activity of ibrutinib in previously untreated and relapsed or refractory CLL with *TP53* aberrations. The primary endpoint was overall response to treatment after six cycles of therapy at 24 weeks. Secondary endpoints were safety, OS, PFS, best response, and nodal response. The study was followed up to 5 years to investigate long term efficacy and safety, as well as depth and durability of the response to treatment, considering MRD remission in the patient cohort.
Mato (2018)	Mato, A. R. et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. Am J Hematol 93, 1394-1401 (2018).	The study of Mato et al. is a US multicentre, retrospective, observational cohort study. Investigators utilised chart review, electronic medical records, and related databases to obtain information of CLL patients in the first-line setting from 20 community and academic centres. Patients included represented patients who were excluded from the RESONATE 2 trial, due to age or presence of the del(17p)/*TP53* mutation. Information on efficacy outcomes and toxicities were also collected.

Abbreviations: CLL: chronic lymphocytic leukaemia; ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival; SLR: systematic literature review.

B.2.9.2 Feasibility assessment: del(17p)/*TP53* population

In the absence of head-to-head randomised controlled trials and head-to-head observational studies, indirect treatment comparisons (ITCs) can be performed across studies to estimate relative treatment effects. However, the results of these analyses can be biased by cross-trial differences in patient populations, sensitivity to modelling assumptions, and differences in the definitions of outcome measures. Incorporating individual patient data (IPD) can address several limitations that arise in analyses which are based on aggregate data only, e.g. the risk of underestimation of the covariate effect and aggregation bias.

The matching adjusted indirect comparison (MAIC) method proposed by Signorovitch et al.[82] is designed to adjust for potential biases which may occur due to differences in patient characteristics across different samples. There is no common comparator between VenG and ibrutinib in the trials identified by the SLR, and so any comparison must be unanchored.

As in any ITC, characteristics of the selected trials must be carefully compared, including the study design, inclusion/exclusion criteria, baseline characteristics, and the included outcomes. Additionally, unanchored MAICs require much stronger assumptions than anchored indirect comparisons as they effectively assume that absolute outcomes (such as median survival or trajectory of the Kaplan–Meier curve) can be predicted from the covariates; that is, they assume that all effect modifiers and prognostic factors can be accounted for using covariates and definitions available in the CLL14 data and published comparator data. This assumption is very strong, and largely considered impossible to meet (NICE technical support document 18 guidance).[83] Failure of this assumption leads to an unknown amount of bias in the unanchored estimate.

For the reasons set out above, a feasibility assessment was performed to evaluate the available evidence obtained from the CLL14 and the comparator data to determine the suitability of the available data for conducting a MAIC of VenG versus ibrutinib for the treatment of FCR/BR-unsuitable, untreated patients with CLL who have del(17p)/*TP53* mutation. The feasibility assessment involved the following steps:

- **Step 1:** Selection of appropriate comparator data.
- **Step 2:** Review of the CLL14 trial and the comparator data sources in terms of the trial design, inclusion criteria, outcome and baseline patient characteristics to estimate potential prognostic variables and effect modifier for PFS and OS.

The four ibrutinib data sources,[60, 71-73] were evaluated for inclusion in a MAIC if they met the criteria outlined below:

- Include the population of previously untreated CLL patients who are unsuitable for FCR and BR with del(17p)/*TP53* mutation and treated with ibrutinib
- Report outcome (PFS and/or OS) for the population of interest
    - Or report outcomes similarly defined as the CLL14 trial and include a Kaplan–Meier plot for PFS and OS, clearly displaying the survival and progression events and numbers at risk for the ibrutinib treatment

- Report baseline clinical characteristics for the population of interest. Although this criterion was only applied to critically appraise reliability of results and not to exclude sources from the analysis.

Population of interest

The target population consists of previously untreated CLL patients with del(17p)/*TP53* mutation. The CLL14 trial included previously untreated CLL patients unsuitable for FCR/BR. The patients without del(17p)/*TP53* mutation need be excluded from the CLL14 trial to match the population of interest. This resulted in the removal of 192 patients in the VenG arm, bringing the total down to 24 patients (Table 24).

This reduced sample was carried forward for subsequent feasibility assessment. As previously mentioned, the ALLIANCE study was excluded from consideration due to small sample size of the del(17p) subgroup (n<10 patients). Of the three remaining ibrutinib data sources, Mato et al.[60] included patients in the previously untreated setting, while the study by Farooqui et al.[72] and Ahn et al.[71] included both patients with previously untreated CLL as well as patients with relapsed/refractory CLL but reported subgroup data based on the previously untreated patients. In the Mato et al. publication, 110 patients were identified with the del(17p)/*TP53* mutation, however, it is unknown how many patients in this group were 65 years and older.[60] Based on the total population included in this study, it was assumed about 59% were aged 65 years and above.

Table 24: Population sizes in CLL14 and comparator trials

Population	CLL14[1]	Ahn et al.[71]	Farooqui et al.[72]	Mato et al.[60]
Total population	216	86	51	391
Non-del(17p)/*TP53* subgroup	192	35	0	281
del(17p)/*TP53* subgroup regardless of line of treatment (first-line or R/R)	24	51	51	110

Abbreviations: R/R: relapsed or refractory.

Outcomes

In the CLL14 trial, both the median PFS and the median OS for the population of interest were not reached in the VenG arm. In the Mato et al. study,[60] both the median PFS and the median OS were not reached. The study by Farooqui et al.[72] and Ahn et al.[71] reported the Kaplan–Meier estimates of PFS and OS for previously untreated CLL patients with *TP53* aberrations, which is inclusive of del(17p). Mato et al. reported Kaplan–Meier curves of PFS and OS, stratified for del(17p)/*TP53* status, and stratified for age.[60]

Baseline or disease characteristics

Matching variables are baseline patient or disease characteristics that have the potential to modify the treatment effect. NICE guidance on “Methods for population-adjusted indirect comparisons in submissions to NICE” suggests that the choice of variables to be matched/weighted on should be carefully considered: including too many variables will reduce

the effective sample size, negatively affecting the precision of the estimate; conversely, failure to include relevant variables will result in a biased estimate.[83]

To further examine the feasibility of conducting a MAIC in the CLL14 trial, an overview of patient characteristics for the population of previously untreated patients with del(17p)/*TP53* mutation and the overview of patient characteristics for the ibrutinib data sources, including Farooqui et al.,[72] Ahn et al.[71] and Mato et al.,[60] are presented in Table 25.

Table 25: Summary of patient baseline characteristics for patients with del(17p)/*TP53* mutation in CLL14 trial and comparator studies

Covariate	CLL14[1]		Farooqui et al.[72]		Ahn et al.[71]		Mato et al.[60]	
	Value	N	Value	N	Value	N	Value	N
Age								
Median (range)	[redacted]	24	62 (33–82)	35	62 (33–82)	51	NR	110
≥65 years of age (%)	[redacted]	[redacted]	NR	NR	41.2%	21	NR	NR
<65 years of age (%)	[redacted]	[redacted]	NR	NR	58.8%	30	NR	NR
Gender								
% male	[redacted]	[redacted]	65.7%	23	60.8%	31	NR	NR
Prior treatment status								
Treatment naïve (%)	100%	24	NR	NR	68.6%	35	NR	NR
CIRS score, N (%)								
≤6	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
>6	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
ECOG, N (%)								
0	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
1	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
2	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
IGHV mutation, N (%)								
Unmutated	[redacted]	[redacted]	62.9%	22	66.7%	34	NR	NR
Mutated	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Creatinine clearance								
<70 mL/min	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
≥70 mL/min	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR

Abbreviations: CIRS: cumulative illness rating scale; del(17p): chromosome 17p deletion; ECOG: European Cooperative Oncology Group; *IGHV*: immunoglobulin heavy-chain variable region; NR: not reported.
Source: AbbVie Data on File (CLL14 Clinical Study Report),[70] Farooqui et al. 2015,[72] Ahn et al. 2018,[71] Mato et al. 2018[60]

The CLL14 trial included the population information for previously untreated CLL patients who are unsuitable for FCR/BR treatment, however, the populations of interest were different across the three ibrutinib studies. All three studies reported on populations with *TP53* aberrations, but none of the studies collected information about cumulative illness rating scale (CIRS) and therefore no data were available for patients unsuitable for FCR/BR treatment with del(17p)/*TP53* mutation to match the CLL14 population. In particular, Farooqui et al. reported on patients with previously untreated CLL patients with *TP53* and del(17p),[72] while the Ahn et al. reported on the CLL patients with *TP53* aberrations (see Table 25).[72 71] Mato et al. reported PFS and OS stratified for del(17p) status and stratified for age, but not the combination of these two characteristics.[60] In addition, the categorical variable age (65 years threshold) was reported in the study by Ahn et al., however, it did not provide subgroup analysis based on the older patients.[71]

To summarise, none of the four sources reported prognostic characteristics for the del(17p)/*TP53* population to allow a meaningful match-adjustment to CLL14 trial characteristics. Specifically, Ahn et al. and Farooqui et al. did not report on the required matching variables including age, gender and *IGHV* mutation status for the del(17p) mutated group, the few reported characteristics from those sources were for those patients with TP53 abberations;[71, 72] and Mato et al. did provide results on the del(17p)/*TP53* population but did not provide any information on baseline prognostic factors.[60]

Conclusions

Of the ibrutinib data sources, no study reported the outcomes for the target population since none of the data sources collected information on the CIRS score. For VenG, the number of eligible patients was only 24. Moreover, matching and weighting patients in the MAIC may reduce the effective sample size in the patient level data for all comparisons. In such a case, the findings from the MAIC may suffer from a lack of statistical power due to a small sample size being available. The estimates of relative treatment effect may become inflated or unstable as they depend heavily on just a small number of individuals.

Furthermore, unanchored comparisons must include every effect modifier and prognostic variable – compared to the anchored case, where only effect modifiers are required. An immediate consequence of this is that an unanchored indirect comparison performed using population-adjustment will always have less precision than an anchored indirect comparison in the presence of imbalanced prognostic variables, and – more importantly – is more likely to be biased given that all prognostic variables as well as effect modifiers in imbalance must be included in the weighting model (while some of them could be unobserved and thus impossible to include in the adjustment model). As such, results from unanchored analyses should be interpreted with high degree of caution in their transposability to the target population, given the high possibility of unaccounted unobserved residual bias.

To conclude, the feasibility assessment suggests that it would not be feasible to use an unanchored MAIC to estimate the relative effectiveness of ibrutinib versus VenG, for the treatment of CLL patients with the del(17p)/*TP53* mutation. As such, an alternative approach was chosen, and an unadjusted naïve indirect comparison, where key prognostic factors are not adjusted for, was therefore performed, using Ahn et al. and Mato et al.[60, 71] Farooqui et al. was not considered further since evidence from this source were captured by Ahn et al., which provides more recent evidence from the same Phase 2, single-arm trial. This decision is also in

line with previous NICE appraisals, including the appraisal, TA429, for ibrutinib in relapsed or refractory CLL, which highlighted that evidence for the del(17p)/*TP53* population treated with ibrutinib is lacking.[3, 34] The committee agreed that the Farooqui et al.[72] study should not be used in the appraisal due to a very limited sample size (N=51), and so a naïve comparison was not conducted for this trial.[34] In this submission, Mato et al. 2018 was considered the preferred study for comparison due to the larger sample size and so is therefore presented in Section B.2.9.3 below. The alternative naïve indirect comparison to Ahn et al. 2018 is presented in Appendix D.

B.2.9.3 Unadjusted naïve indirect comparison (Mato et al. 2018)[60]

In this section, unstratified Cox regression models were applied to estimate the relative effectiveness, in terms of PFS and OS, of VenG versus ibrutinib in CLL patients with del(17p)/*TP53* mutation, using data from the CLL14 trial and data from the Mato et al. publication.[60, 70]

Methods

If the inclusion/exclusion criteria between the CLL14 trial[70] and the Mato et al. study[60] are not the same, there may exist patients in the CLL14 trial who would not have been eligible to compare the Mato et al. data, and hence may contribute bias to the results. Therefore, these patients were removed from the IPD before proceeding with the comparison process.

For the VenG arm, the IPD are available in the CLL14 trial. However, for the ibrutinib arm, the IPD from the Mato et al. study is not assessable. Hence, the available Kaplan–Meier curves were digitised using WebPlotDigitizer[84] to simulate the patient level data from the Mato et al. publication using the methodology developed by Guyot et al.[85] Next, the two datasets were merged. The unstratified Cox regression models were then used to compare between the VenG arm in the CLL14 trial and the ibrutinib arm in the Mato et al. study to calculate PFS and OS hazard ratios. Further details on this process are outlined in Appendix D.

Results

Alignment of inclusion/exclusion criteria

Firstly, patients without del(17p)/*TP53* mutation were excluded, reducing the sample size of the population of interest to 24 for the VenG arm from the CLL14 trial and 110 for the ibrutinib arm from the Mato et al. study.[60] As can be observed in Table 25, the inclusion and exclusion criteria between the CLL14 trial and the Mato et al. publication were different.[60, 70] The Mato et al. publication included patients of all ages, while the CLL14 trial only included patients aged 65 and above.

The inclusion of younger patients in the Mato et al. study could drive the results of the relative comparison to the CLL14 data and generate a trend of ibrutinib superiority.

Unadjusted hazard ratio of PFS

Table 26 and Figure 16 show the results for PFS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation. The HR of [redacted](95% CI: [redacted]) suggests ibrutinib has [redacted]PFS compared with VenG. However, there is [redacted]with respect to the treatment effect (log rank test: p=[redacted]).

This trend should not be considered robust according to the summary statistics and broad confidence internals which demonstrate that in some instances VenG could also be considered superior (by testing the upper bound in the model's probabilistic sensitivity analysis [PSA] simulations). Those key factors lead to the conclusion that the point estimate cannot be considered reliable or robust, alongside the fact that the proportional hazards assumption does not hold (curves cross; Figure 16).

Table 26: Unadjusted hazard ratio of PFS between ibrutinib (Mato et al. study) and VenG

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value
Ibrutinib (VenG reference)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 16: Unadjusted hazard ratio of PFS between ibrutinib (Mato et al. study) and VenG (CLL14)

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Unadjusted hazard ratio of OS

Table 27 and Figure 17 show the results for OS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation. The HR of [redacted](95% CI: [redacted]

[redacted]) suggests VenG has [redacted]OS than ibrutinib. However, there is [redacted] [redacted]with respect to the treatment effect (log rank test: p=[redacted]).

Table 27: Unadjusted hazard ratio of OS between ibrutinib (Mato et al. study) and VenG

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value
Ibrutinib VenG (reference)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; VenG: venetoclax with obinutuzumab.

Figure 17: Unadjusted hazard ratio of OS between ibrutinib (Mato et al. study) and VenG

[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; OS: overall survival; VenG: venetoclax with obinutuzumab.

B.2.9.4 Unadjusted naïve indirect comparison (Ahn et al. 2018)[71]

A secondary unadjusted naïve indirect comparison was also conducted with the study by Ahn et al.[71] As noted above, this is presented in Appendix D.

B.2.10 *Adverse reactions*

B.2.10.1 Safety results informing the decision problem

The safety analyses are based on the safety-evaluable population, i.e. patients who received at least one dose of study treatment (venetoclax, obinutuzumab or chlorambucil) (N=214 in GClb arm and N=212 in VenG arm). Only treatment-emergent adverse events are described hereafter (i.e. any event not present prior to the initiation of study treatment, or any event already present that worsens in either intensity or frequency following exposure to study treatment) and are referred to as AEs throughout. All AEs were to be reported until 28 days after the last dose of venetoclax, chlorambucil, or obinutuzumab.

B.2.10.2 Treatment exposure

VenG combination treatment was completed by [redacted] of the [redacted] who received both agents while venetoclax single agent treatment was completed by [redacted] of the [redacted] patients who started the single-agent period. The median duration of exposure to venetoclax, from first venetoclax dose, was [redacted] days ([redacted] months) (range: [redacted] days [[redacted] months]). After reaching the target dose, the median dose intensity for venetoclax was [redacted] (range: [redacted] %).

Of the [redacted] patients who initiated venetoclax, [redacted] reached the target dose of 400 mg. [redacted] patients did not reach the 400 mg target dose due to a variety of reasons including AEs leading to venetoclax withdrawal and withdrawal of consent from further study participation.

After reaching the target dose of 400 mg, [redacted] patients (43.3%) had a dose modification (i.e. dose interruption or reduction); [redacted] patients ([redacted] %) had dose modification due to an AE.

Of the [redacted] patients with a dose reduction from target dose of 400 mg, [redacted] ([redacted] %) subsequently withdrew from treatment and [redacted] ([redacted] %) returned to 400 mg (see summary of patient status after dose reduction). The remaining patients ([redacted] patients [[redacted] %]) stayed at the reduced level. The median duration of treatment below the 400 mg target dose (in those patients who reached the target dose) was [redacted] days. [redacted] patients had a dose reduction to 50 mg (median duration [redacted] days).

For obinutuzumab, the median dose intensity, cycles and median cumulative dose were [redacted] in both arms: median dose intensity was 100% (range: 0%–111%), patients received a median of [redacted] cycles (range: [redacted]), and the median total cumulative dose was [redacted] mg. The percentage of patients with a dose modification was [redacted] in the GClb arm than in the VenG arm ([redacted] [[redacted] compared with [redacted] [[redacted] %], respectively). Most dose modifications were due to AEs ([redacted] patients [[redacted] %] in the GClb arm vs [redacted] patients [[redacted] %] in the VenG arm).

The median dose intensity for chlorambucil in the GClb arm was 95.4% (range: 4%–111%). Patients had a median of [redacted] cycles of chlorambucil (range: [redacted]). Dose modifications were reported in [redacted] patients (26.9%), with approximately half of these having a dose modification due to an AE ([redacted] patients [[redacted] %]).

B.2.10.3 Treatment-emergent adverse events

Up until the clinical cut-off, 213 patients (99.5%) in the GClb arm experienced [redacted] AEs and 200 patients (94.3%) in the VenG arm experienced [redacted] AEs.

The incidence of Grade 3 or 4 AEs (by the National Cancer Institute common terminology criteria for adverse events [NCI-CTCAE] grading) was similar in both arms: 164 patients (76.6%) in the GClb arm and 167 (78.8%) in the VenG arm.

Individual Grade 3–4 AEs with an incidence of at least [redacted] higher in the VenG arm were neutropenia, hyperglycaemia, diarrhoea and hypertension and are presented in Table 28. Individual Grade 3–4 AEs with an incidence of at least 5% in either arm, which are used to inform the economic model, are presented in Table 29.

Table 28: Grade 3–4 AEs with a difference of at least 2% between treatment arms

	VenG (N=212)	GClb (N=214)	All Patients (N=426)
Total number of patients with at least one Grade 3–4 AE	[redacted]	[redacted]	[redacted]
Overall total number of events	[redacted]	[redacted]	[redacted]
Blood lymphatic system disorders			
Neutropenia	112 (52.8)	103 (48.1)	215 (50.5)
Leukopenia	5 (2.4)	10 (4.7)	15 (3.5)
Metabolism and nutrition disorders			
Hyperglycaemia	8 (3.8)	3 (1.4)	11 (2.6)
Gastrointestinal disorders			
Diarrhoea	9 (4.2)	1 (0.5)	10 (2.3)
Vascular disorders			
Hypertension	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70]

Table 29: Key treatment emergent Grade 3–4 AEs with an incidence of ≥1% in either arm (utilised in cost-effectiveness model)

AE incidence	VenG	GClb
Asthenia	2.40%	0.50%
Diarrhoea	4.20%	0.50%
Dyspnoea	2.40%	0.50%
Febrile neutropenia	5.20%	3.70%
Infusion related reaction	9.00%	9.80%
Leukopenia	2.40%	4.70%
Neutropenia	52.80%	48.10%
Pneumonia	4.20%	4.20%
Sepsis	3.30%	0.90%
Thrombocytopenia	13.70%	15.00%

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

Source: Fischer et al. 2019,[1] AbbVie Data on File (CLL14 Clinical Study Report)[70]

Serious adverse events

The frequency of patients with SAEs was numerically higher in the VenG arm (104 patients [49.1%]) compared with the GClb arm (90 patients [42.1%]).

The most frequently reported SAEs (>2%) were infusion-related reactions (13 patients [6.1%] in the GClb arm and 9 [4.2%] in the VenG arm), pneumonia (9 [4.2%] and 10 [4.7%]), febrile neutropenia (8 [3.7%] and 11 [5.2%]) and pyrexia (7 [3.3%] and 8 [3.8%]). SAEs with an incidence rate of ≥1% of patients are presented in Table 30.

Table 30: Overview of SAEs with an incidence rate of ≥1% of the patients in either treatment group

	VenG (N=212)	GClb (N=214)
At least one serious adverse event – no. of patients (%)	104 (49.1)	90 (42.1)
Serious adverse events with an incidence rate of ≥1% in any treatment group – no. of patients (%)		
Infections and infestations		
Pneumonia	10 (4.7)	9 (4.2)
Sepsis	6 (2.8)	2 (0.9)
Cellulitis	3 (1.4)	0
Injury, poisoning, and procedural complications		
Infusion-related reaction	9 (4.2)	13 (6.1)
Blood and lymphatic system disorders		
Febrile neutropenia	11 (5.2)	8 (3.7)
Thrombocytopenia	2 (0.9)	5 (2.3)
Neutropenia	3 (1.4)	1 (0.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Squamous cell carcinoma of skin	2 (0.9)	3 (1.4)
General disorders and administration site conditions		
Pyrexia	8 (3.8)	7 (3.3)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	3 (1.4)	2 (0.9)
Cardiac disorders		
Atrial fibrillation	1 (0.5)	3 (1.4)
Cardiac failure	3 (1.4)	1 (0.5)
Myocardial infarction	1 (0.5)	3 (1.4)
Metabolism and nutrition disorders		
Tumour lysis syndrome	1 (0.5)	4 (1.9)
Investigations		
Aspartate aminotransferase increased	0	4 (1.9)
Alanine aminotransferase increased	0	3 (1.4)

Abbreviations: GClb: chlorambucil with obinutuzumab; SAE: serious adverse event; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019.[1]

Patient Deaths

In the ITT population, there were 17 deaths in the GClb arm (1 patient died prior to receiving treatment) and 20 in the VenG arm. The overall incidence of deaths reported in the safety evaluable population was comparable between study arms: 16 patients (7.4%) in the GClb arm compared with 20 patients (9.3%) in the VenG arm. The reasons for death are outlined in Table 31.

Table 31: Reasons for death split by treatment period (safety evaluable population)

Period in which death occurred:	Number of patients	
	VenG	GClb
Any time during study (overall)		
Disease progression	[redacted]	[redacted]
Fatal AEs	16	8
Other	[redacted]	[redacted]
Total during study	20	16
During treatment (within 28 days after last dose of study drug)		
Disease progression	[redacted]	[redacted]
Fatal AEs	5	4
Other	[redacted]	[redacted]
Total during treatment	[redacted]	[redacted]
After treatment (after 29 days after the last dose of study drug)		
Disease progression	[redacted]	[redacted]
Fatal AEs	11	4
Other	[redacted]	[redacted]
Total after treatment	[redacted]	[redacted]

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: Fischer et al. 2019[1], AbbVie Data on File (CLL14 Clinical Study Report)[70]

The frequency of fatal AEs was numerically higher in the VenG arm (16 [7.5%]) than in the GClb arm (n=8 [3.7%]). The most frequently reported AE leading to death was sepsis (1 patient [0.5%] in the GClb arm and 5 patients [2.4%] in the VenG arm). Cardiac arrest was reported in 1 patient in each arm.

Of the 16 patients who experienced Grade 5 AEs in the VenG arm, 2 patients who experienced fatal AEs discontinued obinutuzumab prior to receiving the first administration of venetoclax. In both cases, the investigator attributed a causal relationship to obinutuzumab. The other 3 fatal events with onset during the treatment period were sepsis (2 patients) and infection (1 patient). The onset of the remaining 11 fatal AEs occurred in the post-treatment period, that is, 29 days or more after the last study drug administration. In [redacted] of these fatal events with onset post-treatment ([redacted]), the investigator did not attribute a causal relationship with venetoclax treatment.

In the GClb arm, of 8 patients with fatal AEs, 4 had onset during the treatment period, and 4 had onset in the post-treatment period.

Overall, investigators determined that a causal association with venetoclax for the trial deaths appeared unlikely due to the long latency period from the last dose of study drug, relevant pre-existing medical conditions, and concomitant comorbidities/risk factors.

B.2.11 *Ongoing studies*

The CLL14 trial presented in this submission will have further data cuts, however it is not yet possible to confirm when these will become available.

There is currently one additional ongoing study investigating VenG. The GAIA (CLL13) trial is evaluating if standard chemo-immunotherapies (FCR, BR) in treatment of previously untreated physically fit CLL patients without del(17p)/*TP53* mutation can be replaced by combinations of targeted drugs with anti-CD20-antibodies (VenG, venetoclax with rituximab, or venetoclax with obinutuzumab and ibrutinib).

B.2.12 *Innovation*

Venetoclax is a first-in-class, oral, selective inhibitor of B-cell lymphoma 2 (Bcl2), with a unique targeted mechanism of action that distinguishes it from other available therapies. The innovative potential of VenG, as demonstrated in the CLL14, trial can be summarised as follows:

- **VenG is effective in patients both with and without del(17p)/*TP53* mutation.** As demonstrated in Section B.2.7, VenG showed superior PFS efficacy compared with GClb in del(17p)/*TP53* mutation patients as with the overall trial population.
- **VenG increases the range of treatment options in the FCR/BR-unsuitable (elderly and comorbid) population.** Most CLL patients are older than 70 years and often have coexisting conditions, and so there is an unmet need for a broader range of therapeutic options: VenG helps to address this.
- **VenG has a manageable side-effect profile.** As demonstrated in Section B.2.9.1, the safety and tolerability of VenG are overall predictable, acceptable, manageable and therefore tolerable.
- **VenG results in significant rates of undetectable MRD.** MRD is an objective measure of disease status and presence of undetectable MRD indicates the depth of remission; patients achieving undetectable MRD levels are likely to have a long, treatment-free remission. In addition to the benefits received by patients, there are benefits to the healthcare system in the form of budget certainty and a delay to requiring the next line of treatment.
- **VenG is a fixed treatment duration (12 cycles), chemo-free therapy.** This enables significant proportions of patients to experience a prolonged period of time without therapy, reducing the overall, significant cost burden of therapy, especially when contrasted to daily, treatment-to-progression therapies such as BCRis. The fixed treatment duration also has the potential to improve treatment adherence and reduce the risk of mechanism-induced drug resistance.
- **VenG avoids the need for chemo-immunotherapy.** Early intervention with chemotherapy has been shown to not improve the natural history of CLL and may drive clonal evolution and later treatment resistance.[38, 49, 50]

In conclusion, the CLL14 trial provides evidence that VenG is an effective treatment in both patients with and without del(17p)/*TP53* mutation, providing a cost-effective and valuable alternative to current first-line treatment options. Furthermore, VenG has the potential to provide substantial health-related benefits in the form of a fixed-treatment duration chemo-free therapy, with a manageable side effect profile. This enables a significant proportion of patients prolonged time without therapy, reducing the overall cost burden of treatment.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principle findings from the clinical evidence base

There are limited treatment options available for untreated CLL, with few licensed therapies currently used in UK clinical practice. Chlorambucil based chemo-immunotherapies are the backbone of treatment in FCR/BR-unsuitable patients without del(17p)/*TP53* mutation, however there is an unmet need for a broader range of therapeutic options with a different mechanism of action,[2] particularly those with a safety profile suitable for elderly or FCR/BR-unsuitable patients. While BCRis such as ibrutinib have reduced the reliance on toxic chemo-based therapies in the first-line del(17p)/*TP53* mutation population, there is an unmet need for patients with cardiac risk factors or bleeding risk who cannot tolerate ibrutinib.[2] The high unmet needs of CLL patients due to the lack of treatment options is further compounded by the fact that most CLL patients are older than 70 years (median age at diagnosis is 72 years) and often have clinically relevant coexisting conditions, which limit the extent to which currently available therapies can be used.[17, 24, 25]

VenG offers a highly effective chemotherapy free treatment option for patients with untreated CLL. Evidence from the CLL14 trial suggests that VenG leads to better survival outcomes, which is best illustrated by the observed Kaplan–Meier PFS curves. After a median follow up of 28.1 months, the investigator-assessed PFS was both statistically significant ($p<0.0001$) and clinically meaningful with a considerable and meaningful reduction in the risk of disease progression or death in patients receiving treatment with VenG compared to patients receiving treatment with GClb (stratified HR 0.35; 95% CI: 0.23, 0.53). The benefit of VenG over GClb was confirmed by an independent review committee (IRC) assessment of PFS and other secondary efficacy end points. There is also evidence of eradication of detectable disease (undetectable MRD) which allows VenG to be administered as a time-limited therapy and prolongs the length of treatment-free remission.

Notably, these results were observed in a multinational setting, with a safety profile of the combination that is acceptable, predictable and generally consistent with the known safety profiles of venetoclax and obinutuzumab as single agents. Neutropenia is a known adverse effect of venetoclax, and the higher rates of grade 3 or 4 events that were observed in the VenG arm compared with GClb (52.8% of patients versus 48.1%, and 5.2% versus 3.7% for febrile neutropenia) were not unexpected. With standard of care measures including dose modifications and use of GCSF, neutropenia was manageable, with few patients discontinuing treatment for neutropenia ([redacted] in the VenG arm and [redacted] in the GClb arm). The relatively small number of patients in the VenG group who had tumour lysis syndrome (TLS) (3 patients compared with 5 patients in the GClb arm) shows the effectiveness of the risk mitigation procedures that were implemented during the trial and the generally manageable and safe

delivery of the treatment. None of the TLS events met the Howard criteria for clinical TLS (i.e. the presence of specific electrolyte changes and clinical manifestations).

For the population of patients with del(17p)/*TP53* mutation, a feasibility assessment determined there was insufficient data on CLL patients receiving ibrutinib as first-line treatment to allow for an adjusted comparison. Unadjusted HRs between ibrutinib, using the publication from Mato et al.,[60] and VenG were calculated as [redacted] for PFS (95% CI: [redacted]; p=[redacted]), and [redacted] for OS (95% CI: [redacted]; p=[redacted]), however none of the results were statistically significant due to the small population sizes included in the analysis. The differences in potentially confounding baseline factors were also not balanced between the trials in analyses. This result should be interpreted in the context of a general paucity of evidence in the first-line del(17p)/*TP53* setting. It should be noted that NICE previously recommended ibrutinib treatment in this indication (TA429) based on efficacy outcomes in the relapsed/refractory setting since there was no evidence in the first-line del(17p)/*TP53* setting, which demonstrates the high unmet need in this sub-population. Outcomes from the CLL14 trial demonstrate that VenG is also an effective treatment for patients with del(17p)/*TP53* mutation, helping to address some of the high unmet need particularly experienced by this population, by providing an additional therapeutic option.

B.2.13.2 Strengths and limitation of the evidence base

Internal validity of CLL14

As discussed in Section B.2.5, the CLL14 trial was methodologically robust and well reported. The results were considered to be at low risk of bias:

- Participants were appropriately randomised using an interactive voice response system
- The sample size was sufficient to detect a difference in the primary objective of investigator-assessed PFS between the two treatment groups
- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation
- The primary outcome of investigator-assessed PFS was further assessed and confirmed by an IRC

External validity of CLL14

The results of the CLL14 trial can be generalised to the UK population, considering there was a high proportion of Caucasian patients; additionally, 6 investigation sites were in the UK. This assumption was validated by UK clinicians at an AbbVie run advisory board. The results are also well aligned with the decision problem specified in the NICE scope.[4] The external validity of the CLL14 trial is supported by the following:

- **Population** – The study population of CLL14 was defined as patients with previously untreated CLL according to the iwCLL criteria.[35] Most CLL patients are older than 70 years (median age at diagnosis is 72 years) and have clinically relevant coexisting conditions.[17, 24, 25] This was reflected in the CLL14 study, where the median age of patients was 72 years and [redacted] (in the GClb group) reported a concurrent medical condition at baseline. The

CLL14 study population is relevant to the epidemiology of CLL in the UK. The population included patients from six clinical trial sites across the UK.

- **Intervention and Comparators** – VenG was directly evaluated as a treatment option for patients with previously untreated CLL by comparing VenG directly to comparator GClb. The GClb dose used is similar to that used in routine clinical practice, except that 12 cycles of chlorambucil were used in this trial rather than 6 cycles which tend to be used in NHS practice. The choice of GClb as comparator in the trial aligns with the current NHS standard of care for this population.
- **Outcomes** – A wide range of outcomes were evaluated, including all outcomes outlined in the scope that are relevant to patients and to clinicians (PFS, OS, response rates, MRD, HRQoL and safety).

Comparing the CLL14 trial to the CLL11 trial allows external validation of the results of common GClb arm. The CLL11 trial previously showed a median PFS of 31.5 months, with approximately 49% of patients who received GClb surviving without progression at 30 months.[54, 86] In CLL14, the median PFS in the GClb group was not reached, and 60% of the patients receiving GClb were surviving without progression at 30 months, most likely because of the 6-months-longer treatment duration with chlorambucil in the CLL14 trial than in the CLL11 trial. Despite the favourable results in the comparator group, VenG was associated with significantly longer PFS than GClb. Moreover, approximately half the patients in the VenG group had a complete response (49.5%), which compares favourably to other therapies that are frequently used in this older population of patients with CLL.[17]

Limitations

- The OS data obtained from the CLL14 trial was considered too immature to be evaluable at clinical cut-off (median OS was not reached in either arm). However, this is typical in previously untreated CLL: GClb took almost five years to show a difference in OS but the PFS benefit did translate to OS benefit with longer follow-up.[87, 88] Similarly, PFS benefit observed in CLL14 is expected to translate to OS benefit over time and further, scheduled data cuts of CLL14 may reduce uncertainty in OS estimates. Additionally, there is published evidence of a positive correlation between undetectable MRD and prolonged OS[23] which would indicate an OS benefit in the VenG arm, when compared to GClb, could be anticipated due to the superior undetectable MRD results for VenG both on- and off-treatment.
- For the non-del(17p)/*TP53* population, the only trial from which comparison can be made is the CLL14 trial. It is not possible to draw any additional information from other trials as there are no connected trials. However, this was a large, well-designed trial at low risk of bias, providing sufficient comparison of the two treatments.
- As discussed earlier, there is a general paucity of evidence in the del(17p)/*TP53* population. Thus, the results for the unstratified Cox regression model used to estimate the HRs for PFS and OS between VenG and ibrutinib must be interpreted with caution:
    - Firstly, the comparison of treatment outcomes was performed based on totally separate studies, in which results of individual arms from the CLL14 and the Mato et al. studies, were compared as if they were from the same randomised controlled trial. Because the advantage of the randomised trials is completely disregarded, evidence from this naïve unadjusted indirect comparison is equivalent to evidence from observational studies and has increased susceptibility to bias. The effect of a

treatment may be over- or underestimated because of cross-trial differences in patients' baseline characteristics or differences in outcome definitions, resulting in flawed recommendations for clinical practice. Notably, the differences in inclusion criteria for age, resulting in the population of the Mato et al. study being younger in age suggests the results are likely biased in favour of ibrutinib.

- Secondly, as previously discussed in Section B.2.9, the naïve unadjusted indirect comparison was performed on relatively small sample sizes, and this might have led to limited robustness of the estimates.

B.2.13.3 Conclusion

Considerable unmet need exists for previously untreated CLL patients who are considered unsuitable for FCR and BR as well as those with del(17p)/*TP53* mutation.

The mainstay of current treatment in the non-del(17p)/*TP53* mutation population, GClb, does not provide deep and durable responses for the majority of patients, beginning the cycle of remission and relapse as the disease progresses inevitably without cure. In addition to providing a significant increase in PFS over GClb in this patient population, VenG has been shown to provide deep and durable responses for many patients and a positive recommendation from NICE would lead to a step-change in the management of CLL within the NHS.

For patients with del(17p)/*TP53* mutation, the need for additional treatments is arguably even greater, due to the poor prognostic outcomes for this population (as described in Section B.1.3.1), and that ibrutinib is approved in this population, despite having no data in previously-untreated del(17p)/*TP53* mutated patients. Introduction of VenG would provide an alternative treatment to ibrutinib for these patients, particularly for those patients unable to tolerate ibrutinib, such as those with significant cardiac disease or bleeding risk, and who are left with no alternative treatment option.

B.3 Cost effectiveness

A *de novo* cost-utility analysis was undertaken based on a partitioned survival model, similar to those used in previous NICE appraisals for previously untreated CLL.

- A three-state partitioned survival model was developed to evaluate the cost-effectiveness of VenG in previously untreated CLL from the perspective of the NHS and Personal and Social Services (PSS).
- The three health state divisions (pre-progression, post-progression and death) followed the clinical pathway for untreated CLL patients. Costs and benefits were discounted at a rate of 3.5% and a lifetime-equivalent time horizon was used (30 years).
- Two populations were considered in this analysis, in line with CLL14 trial population and anticipated position of VenG in the clinical pathway: patients without del(17p)/*TP53* mutation and for whom FCR/BR treatment is unsuitable (VenG vs GClb), and patients with del(17p)/*TP53* mutation (VenG vs ibrutinib).
- The clinical outcomes used to inform the model were PFS, TTNT, TOT, OS, occurrence of AEs. Health state utilities were informed by a previous NICE appraisal (TA343, GClb for untreated CLL), due to unexpectedly favourable EQ-5D-3L utility values from the CLL14 trial. Costs and healthcare resource use were captured in the analysis for active treatment, routine care and monitoring and treatment specific monitoring for TLS costs; subsequent treatment costs; and AE management and terminal care costs.

Survival analyses

- The CLL14 trial was considered to provide the most appropriate parameter estimates pertaining to PFS, OS and TTNT. Other sources were also explored for external validation of OS extrapolations with the CLL11 trial of GClb being the trial with characteristics most similar to CLL14 and with a longer follow-up.
- Survival models were selected according to decision support unit (DSU) guidance and those selected as the base case were the ones that gave the most plausible long-term predictions compared with longer-term survival data from external sources (CLL11).
- For the non-del(17p)/*TP53* mutation population, data from CLL14 using an independent model (log-logistic) to inform PFS was used. Due to trial data immaturity, no treatment effect on OS was assumed for VenG and GClb and a dependent model (Exponential) was selected as base case. Time-to next treatment (TTNT) was extrapolated using an independent (Weibull) model applied to CLL14 data for both VenG and GClb arms.
- Due to the limited evidence of ibrutinib in the untreated CLL with del(17p)/*TP53* mutation population, network meta-analyses and matched adjusted comparison were not feasible. A naïve comparison of VenG versus Ibr was performed using the Mato et al. study.[60]
- For both populations, modelling decisions and clinical plausibility of the projections of outcomes was validated by experts and additional approaches were tested in scenario analyses.

Base case analysis

Non-del(17p)/TP53 mutation population

- In the deterministic analysis, VenG dominated GClb
- The key driver of relative cost-effectiveness was the difference in PFS, with a larger proportion of patients remaining progression free in the VenG arm than in the GClb arm. The estimated duration of progression free for VenG patients is [redacted] years and [redacted] years for GClb. As a result, the costs of post-progression health state, driven by costly 2nd line innovative therapies were significantly higher in the GClb arm.
- Average accrued lifetime costs and QALYs in the post-progression/relapse health state were higher than the comparator arm due to [redacted]% (VenG) vs [redacted]% (GClb) of patients in the CLL14 study being at PFS state at year 2 off-treatment which led to an OS almost identical to that of the general population for both arms.

Non del(17p)/TP53 mutation population

- In the base case analysis VenG dominated ibrutinib in the del(17p)/*TP53* mutation population.
- The driver of the incremental cost effectiveness ratio (ICER) values was ibrutinib costs due to the treat-to-progression regimen with a mean treatment duration of (1358 days) compared to VenG fixed-treatment duration of 12 Cycles (295.3 days).

Sensitivity analyses

- Parameter uncertainty was explored through probabilistic sensitivity analysis while structural uncertainty and key assumptions were explored through extensive scenario analyses and deterministic one-way sensitivity analyses.
- Probabilistic ICERs were similar to deterministic ICERs (remaining dominant in both populations), whilst all scenarios tested found VenG to remain cost-effective (mostly dominant), save for unrealistically short model time horizons, demonstrating that ICERs were relatively stable to changes in the methods for survival analysis. As expected, deterministic sensitivity analyses on extreme parameter values found the model to be most sensitive to estimates of age and post-progression survival (PPS) and PFS utility values.
- The scenario analysis demonstrated that VenG is consistently cost-effective when compared to GClb or ibrutinib, with all but one scenario in each population resulting in a positive net monetary benefit.

Conclusions

- Results of the base case analysis show that VenG is a cost-effective option at conventional willingness to pay thresholds in the deterministic and probabilistic analyses.
- Probabilistic sensitivity analyses were consistent with the deterministic results, showing a >90% probability of being cost-effective in both the non-del(17p)/*TP53* and del(17p)/*TP53* populations at the £30,000/QALY willingness to pay threshold.
- Deterministic and probabilistic sensitivity analyses, and additional scenario analyses demonstrated that the model results and conclusions were robust to input range and assumption changes.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted in December 2018 and updated in July 2019 to identify studies assessing the cost-effectiveness of interventions for patients with previously untreated CLL. The SLR identified 43 publications reporting relevant cost-effectiveness analyses. Full details of the methods and results can be found in Appendix G.

None of the cost-effectiveness studies identified in the SLR addressed the decision problem of this submission, and therefore are not relevant to decision making. Full details of all studies identified in the SLR can be found in Appendix G. Previous NICE appraisals in previously untreated CLL were consulted during model development, as noted below.

B.3.2 *Economic analysis*

B.3.2.1 Patient population

The economic evaluation presented in this submission aligns with the decision problem described in Table 2, Section B.1.1, and utilises data from the phase 3 randomised trial, CLL14 (August 2018 data cut: 28.1 months follow-up).

The analysis demonstrates the benefits of VenG compared with relevant treatments for two distinct patient groups:

- Patients without del(17p)/*TP53* mutation, compared with GClb (CLL14;[1] n=387)
- Patients with del(17p)/*TP53* mutation, compared with ibrutinib (CLL14 compared with Mato et al.;[160] n=31)

Mutation status involving del(17p)/*TP53* mutation was combined into a single variable as these are known to share similar prognostic information. This is based on what has been accepted in a previous NICE appraisal,[3] clinical expert opinion and published literature that commonly groups these subpopulations together as patients with TP53 aberrations.[71, 89, 90] The following algorithm was used to assign the subpopulations:

- If del(17p) is abnormal (determined by central lab), variable = 1
- If del(17p) is normal (determined by central lab), variable = 0
- If del(17p) is missing & *TP53* is mutated, variable = 1
- If del(17p) is missing & *TP53* is unmutated, variable = 0
- Else if both are missing = NA (none have both missing)

As a result of this, the population numbers used in the submission differ between the clinical analysis presented in Section B2 and the economic analysis presented in Section B3, and these are shown in Table 32.

Table 32: Population numbers utilised in the CSR and CEM analyses

	CSR Analysis	CEM Analysis
Non-del(17p)/*TP53* mutation	386	387
Del(17p)/*TP53* mutation	46	31
Undefined	0	14
Total	432	432

Abbreviations: CEM: cost-effectiveness model; CSR: clinical study report.

A summary of the CLL14 trial is provided in Section B.2. Key model inputs that differed between the two subpopulations included PFS, time-on-treatment, TTNT, the survival analyses of PFS and OS and incidence of AEs (Section B.3.3.9).

B.3.2.2 Model structure

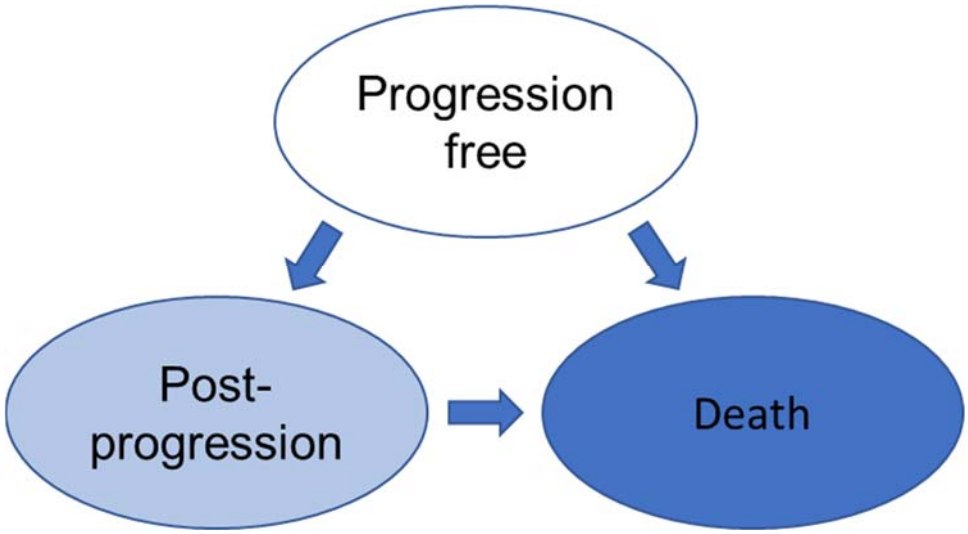
In the partitioned survival approach, the patient pathway is split into PFS, PPS and death, and a three-state partitioned survival model was developed. The design of the model structure was informed by the clinical pathway, clinical expert input, previous CLL models used in NICE appraisals, and with respect to data availability from the trial.[34, 67] Relevant modelled health states are well-established in clinical practice, aligned with CLL14 primary outcomes and defined as follows:

- **Progression-free:** includes patients who are alive and have not progressed.
- **Post-progression survival:** includes patients who are alive but have progressed.

- **Death:** this state is dictated by the overall survival curve, which accounts for the number of patients who have died from either CLL or other causes. To account for death due to other causes, the OS estimates are corrected for background mortality under the assumption that the age- and sex-adjusted mortality risk of CLL patients can never be lower than the age- and sex-adjusted mortality risk of the general population.

The patient population distributions within each health state over time were approximated using extrapolated survival curves. TTNT curves were also used to calculate the timepoint for subsequent treatment initiation and corresponding costs. When modelling the CLL disease pathway, it is important to be sensitive to a patient's progression status, as well as their overall survival. The three states included in the model capture the disease pathway of CLL patients as closely as possible (Figure 18).

Figure 18: Three-state partitioned survival model used in the cost-effectiveness analysis



Costs are considered based on an England and Wales National Health Service (NHS) and Personal and Social Services (PSS) perspective.

A 28-day cycle length is used in the model, which is deemed sufficient to accurately capture the clinical outcomes reported for CLL patients from the pivotal trials. The cycle length also fits with the dosing schedules of VenG and its comparators.

Considering the mean age of patients in CLL14 (71.1 years), patients in the cost-effectiveness model (CEM) are modelled for a lifetime time horizon of maximum 30 years. Based on NICE guidelines, a 3.5% discount rate is applied to the cost and effects outcomes of the model.

A summary of the model characteristics is provided in Table 33.

Table 33: Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	**TA343[67] (GCIb)**	**TA429[34] (ibrutinib)**	**Chosen values**	**Justification**
Time horizon	20-years	20-years	30-years	Aligned with NICE reference case, with the aim to fully capture lifetime costs and benefits
Model structure	Partitioned-survival	Partitioned-survival	Partitioned-survival	In line with previous appraisals
Cycle length	7-days	28-days	28-days	Consistent with the length of treatment cycles of active therapy relevant to the model and short enough to accurately model costs and outcomes
Half-cycle correction	Yes	Yes	Yes	Mitigates bias due to cycle length
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	NICE reference case
Discount of 3.5% for utilities and costs	Yes	Yes	Yes	NICE reference case
Perspective (NHS/PSS)	Yes	Yes	Yes	NICE reference case
PFS extrapolation	Gamma distribution tails fit to the K–M data of the CLL11 trial	Exponential distribution	Independent model, log-logistic distribution	Aligned with advice from NICE DSU: closest to data from external sources and after consultation with clinical and economic experts

	Previous appraisals		Current appraisal	
Factor	**TA343[67] (GCIb)**	**TA429[34] (ibrutinib)**	**Chosen values**	**Justification**
OS extrapolation	OS modelled as from progression and from post-progression. Exponential distribution fit to pooled post-progression rates from the older CLL5 trial, adjusted for age at progression used	Weibull distribution	Dependent model, exponential distribution. No treatment effect assumed	As determined by consultation with clinical and economic experts
ToT extrapolation	Not modelled; drug acquisition costs are adjusted for mean number of cycles (out of the maximum 6) and dose intensity	Patients continue treatment with ibrutinib until progression; treatment discontinuation is informed by treatment discontinuation K–M data from RESONATE, which takes into account dose reduction or discontinuation due to tolerability. Comparators were modelled to be treated until progression or the maximum number of cycles Drug acquisition costs adjusted for dose intensity	Not extrapolated; data used from CLL14 trial in which treatments are given for a fixed duration of 12 months as per protocol	As determined by consultation with clinical and economic experts

	Previous appraisals		Current appraisal	
Factor	**TA343[67] (GCIb)**	**TA429[34] (ibrutinib)**	**Chosen values**	**Justification**
TTNT extrapolation	Not modelled; all participants were thus assumed to receive a course of chlorambucil post-progression, and this was subject to scenario analyses to address potential uncertainty	Based upon the ofatumumab arm of the RESONATE trial it is assumed that 42% of those progressing receive second-line treatment: 50% R-HDMP and 50% HDMP. Proportion remaining on treatment is conditioned by a second PFS curve (Weibull) within the PPS state	Independent model, Weibull distribution	Aligned with advice from NICE DSU: closest to data from external sources and after consultation with clinical and economic experts
Pre-progression utility	On treatment 0.55 (1st dose G) 0.67 (IV Tx) 0.71 (oral Tx) Off-treatment 0.71 to 0.76 (Committee uncertainty)	0.80; benefit of treatment increment added after consultation, Committee remained concerned that the model under-estimated the benefit of ibrutinib	0.670	PFS under IV treatment taken from TA343[67]
Post-progression state utility	PD: 0.60	0.60; age-adjusted	0.600	Weighted average of the following utilities from TA343[67] (progression after first-line treatment, PFS ± second-line treatment, relapsed line of treatment)

	Previous appraisals		Current appraisal	
Factor	**TA343[67] (GClb)**	**TA429[34] (ibrutinib)**	**Chosen values**	**Justification**
Source of AE disutility	Disutilities due to adverse events are not explicitly taken into account	Notes that trial-based utilities may implicitly include AE disutility and therefore modelling disutilities may be double counting; nonetheless these were modelled based on literature values	Disutilities are applied only in the first year of treatment	Disutility values based on previous NICE appraisals

Abbreviations: AE: adverse event; DSU: Decision Support Unit; G: obinutuzumab; GClb: chlorambucil with obinutuzumab; HDMP: high-dose methylprednisolone; IV: intravenous; K–M: Kaplan–Meier; NHS: National Health Service; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; PSS: Personal and Social Service; ToT: time-on-treatment; TTNT: time-to-next treatment; Tx: treatment.

B.3.2.3 Intervention technology and comparators

The intervention undergoing comparison is VenG, as described in Section B.1.2. Venetoclax is an oral tablet and is delivered with an initial dose escalation:

- Cycle 1, Day 22–28: 20 mg daily
- Cycle 2, Day 1–7: 50 mg; Day 8–14: 100 mg; Day 15–21: 200 mg; Day 22–28: 400 mg
- Cycle 3–12, Day 1–28: 400 mg daily

Venetoclax is given for a fixed treatment duration until the end of Cycle 12 based on the clinical trial protocol requirements and as also demonstrated by the mean time on treatment (ToT) derived from the August 2018 data cut from the CLL14 trial (mean ToT for VenG = [redacted] days).

Obinutuzumab is administered as an intravenous infusion. The recommended dosage is 1000 mg administered over Days 1 (100mg) and 2 (900mg), 1000 mg on Day 8 and Day 15 of treatment Cycle 1, followed by 1000 mg on Day 1 of treatment Cycles 2–6. Chlorambucil is given orally as 0.5 mg/kg on Day 1 and Day 15 for Cycles 1−12. Obinutuzumab is also given for a fixed treatment duration which is until end of Cycle 6 based on the clinical trial protocol and as also demonstrated by the mean ToT derived from the August 2018 data cut from the CLL14 trial (mean ToT for GClb = 10.8 months).

There is a difference between the number of cycles of Clb used in the control arm of the CLL14 trial (12 cycles) and the number of cycles of Clb used in UK clinical practice (six cycles).[1] According to UK clinical experts at an AbbVie-organised HTA advisory board, overall dose is likely to have a larger impact on efficacy than the number of cycles. Of note is that the overall dose in the CLL14 trial (70 mg* × 12 = 840 mg, *based on a typical patient with a body weight of 70 kg and height of 170 cm) is comparable to the overall dose used in clinical practice (120 mg* × 6 = 720 mg). The clinical experts suggested that there is good justification for the CLL14 study

design, because the trial design would have appeared biased towards VenG if patients in the VenG arm received 12 cycles of treatment and patients in the GClb arm only received six. The experts concluded that the difference in the number of cycles was not a concern because, if at all, 12 cycles of GClb, as used in the control arm of the CLL14 trial, would most likely lead to better results than six cycles, making the comparison to VenG conservative. Thus, costs of this economic evaluation fully align with CLL14 trial protocol in order to best represent the relative difference in costs as seen in observed data.

Based on NICE and BSH guidelines, and following validation from clinical experts (all as described in Section B.1.3.4 and B.1.3.5), the only two comparators of clinical relevance to VenG in the populations of interest are GClb and ibrutinib.

- GClb is considered as a comparator for patients without del(17p)/*TP53* mutation and for whom FCR/BR treatment is unsuitable.
- Ibrutinib is a comparator for patients with del(17p)/*TP53* mutation.

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

Table 34 presents the patient population characteristics used in the model for both populations considered. These were based on the patients in the CLL14 trial, as presented in Table 9, Section B.2.3.4. The 12 patients in the initial non-randomised safety run-in phase of VenG (Table 7, Section B.2.3.3) were excluded from the analyses of PFS, OS and TTNT. As a result, endpoints for 216 patients in each of the treatment arms (VenG and GClb) were analysed.

For the time-on-treatment endpoint, only patients that were administered venetoclax monotherapy (n=203) in the VenG arm, following six cycles of VenG combination therapy (see trial design, Section B.2.3.1), and chlorambucil (n=212) in the GClb treatment arm, following six cycles of GClb combination therapy, were assessed.

Table 34: CLL14 study data for the two modelled populations

Variable	Application in the model	
	Non-del(17p)/*TP53*	**Del(17p)/*TP53***
Mean age (years)	71.1	69.6
Gender (% male)	66.4%	67.7%
Mean bodyweight (kg)	75.6	78.2
Mean height (cm)	168.8	167.9
Mean body surface area (m^2)*	1.9	1.9
PFS (used for long term extrapolations)	See Section B.3.3.5	See Section B.3.3.9
OS (used for long term extrapolations)	See Section B.3.3.6	See Section B.3.3.9
TTNT (used for long term extrapolations)	See Section B.3.3.7	See Section B.3.3.7
ToT (mean values from trial)	VenG: 314.5 days	VenG: 295.31 days

Variable	Application in the model	
	Non-del(17p)/*TP53*	Del(17p)/*TP53*
	GClb: 300.04 days	Ibrutinib: 1358 days**
AE incidence (TEAE grade 3-4 with >1% incidence)	See Section B.3.3.12	See Section B.3.3.12
Treatment courses (used to calculate costs of first line treatments)	See Section B.3.5.1	See Section B.3.5.1
Utilities (explored in scenario analysis)	See Section B.3.4.1	See Section B.3.4.1

Calculated by the Dubois method: 0.007184(height^0.725)*(weight^0.425)
**The mean ToT for ibrutinib is sourced from the base case PFS analysis using the HR from the Mato et al. publication.[60]
Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; TEAE: treatment-emergent adverse event; ToT: time-on-treatment; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

B.3.3.2 Overview of time-to-event data

Figure 19, Figure 20, Figure 21 and Figure 22 present the Kaplan–Meier curves and numbers at risk for PFS, OS, TTNT and ToT, respectively, for both VenG and GClb over the observed time period in CLL14.

Figure 19 presents PFS data from CLL14 IRC analyses (endpoint used in the economic model) which are consistent with investigator-assessed PFS. The primary efficacy analysis demonstrated a significant PFS benefit (HR 0.35; 95% CI: 0.23, 0.53; p<0.001) for patients in the VenG arm (29 events) compared with patients in the GClb arm (79 events). Although median values were not reached, the difference in PFS is apparent with VenG arm PFS as high as 88.15% at Year 2 vs 64.10% for the GClb arm. It is important to note the clear large separation between arms, especially after the first 12 months of treatment, which drives the extrapolated model outcomes.

Figure 19: Kaplan–Meier IRC-assessed PFS curves for VenG and GClb

Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; IRC: independent review committee; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 20 presents data on OS between arms from CLL14 trial. The overall death rates were similar between arms and although there was a numerically higher number of events in the VenG arm, a causal association with venetoclax was considered unlikely. This trend is explained by confounding factors, such as previous medical history, concurrent illnesses and latency of AE onset following last treatment dose.

Figure 20: Kaplan–Meier OS curves for VenG and GClb

Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

In Figure 21, Kaplan–Meier data from CLL14 on TTNT are presented with 18 fewer patients moving to next treatment for the VenG arm (27 events) compared to GClb (45 events). This trend demonstrates that Venetoclax delays and reduces the need for subsequent treatment.

Figure 21: Kaplan–Meier TTNT curves for VenG and GClb

Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

Figure 22 presents Kaplan–Meier curves for average ToT in each CLL14 treatment arm. Median duration of exposure to venetoclax, from the first venetoclax dose, was [redacted] days and the mean duration was [redacted] days (range: [redacted] days).

Figure 22: Kaplan–Meier ToT curves for VenG and GClb

Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; ToT: time-on-treatment; VenG: venetoclax with obinutuzumab.

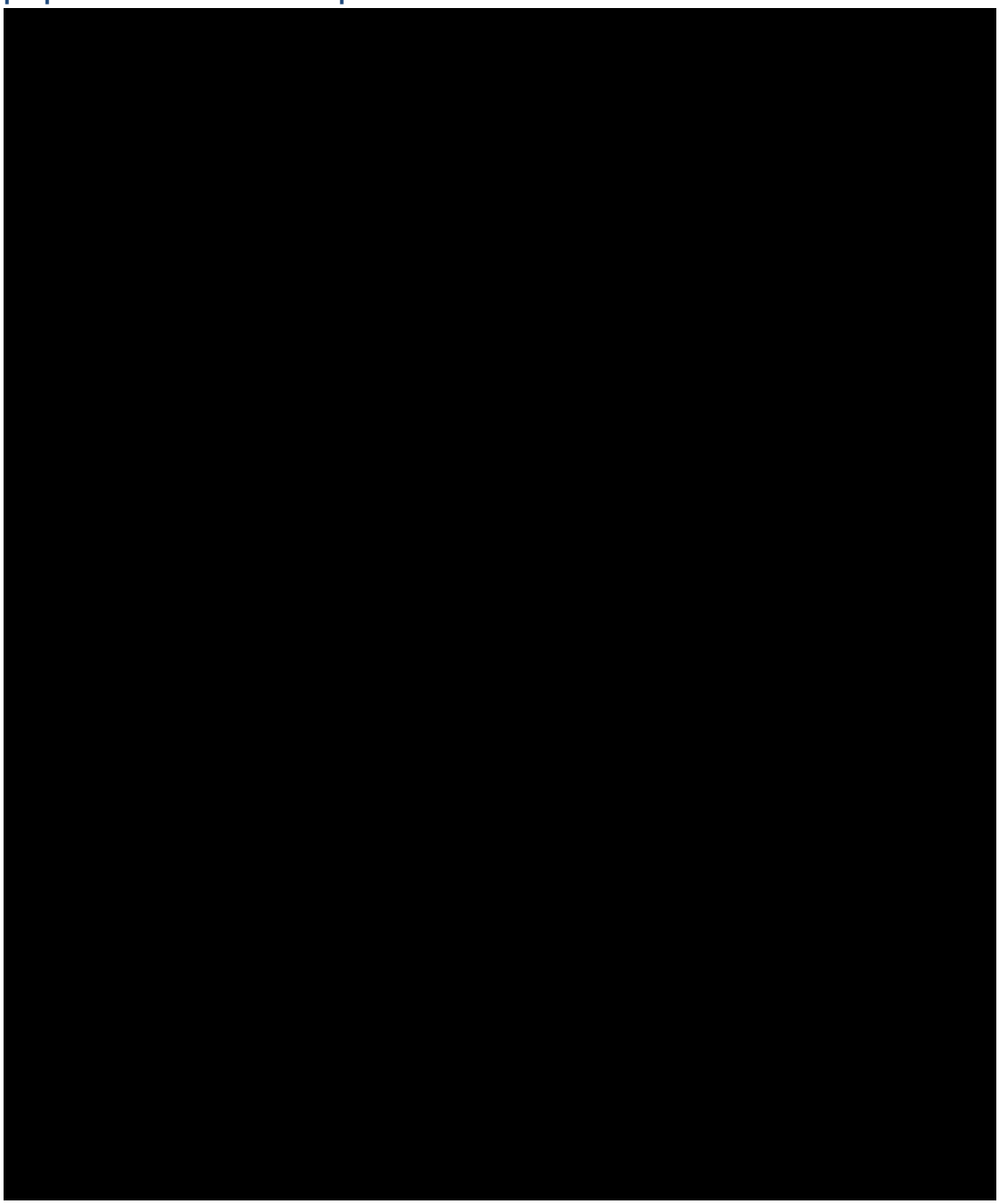
B.3.3.3 Assessing the proportional hazards assumption

To maximise the predictive power of the CLL14 data, assumptions can be made around how various endpoints might be related to one another. The proportional hazards assumption allows one time-to-event curve to be described in terms of another, by assuming an (homogenous in time) proportional relationship between their underlying hazard functions (i.e. a hazard ratio). The key assumption is that the rate of change of hazards remains constant in time, both in the observed period and throughout the unobserved (extrapolated) period which is the model's time horizon (30 years). The validity of this assumption can be explored during the observed period, but the extent it remains valid throughout the predictive horizon remains uncertain.

Exploring proportionality of hazards between treatments

The proportionality of hazards between the two treatment arms VenG and GClb was explored by fitting a Cox proportional hazards model and by evaluating the Schoenfeld residuals.[91] The proportionality of hazards for the two treatments was further assessed by visual inspection of the graph showing the logarithm of the estimated cumulative hazard function. Figure 23 presents the Kaplan–Meier curves for OS and PFS (subfigures A and B) and a visual depiction of the assessment of proportional hazards assumption between VenG and GClb (subfigures C and D). Subfigures C and D present a plot of the scaled Schoenfeld residuals, along with a smoothed curve and the (logged) hazard ratio for reference. The proportional hazards test results in a p value of greater than 0.05 for both OS and PFS.

Figure 23: Kaplan–Meier curves for OS and PFS for VenG and GClb and assessment of proportional hazards assumption between treatments



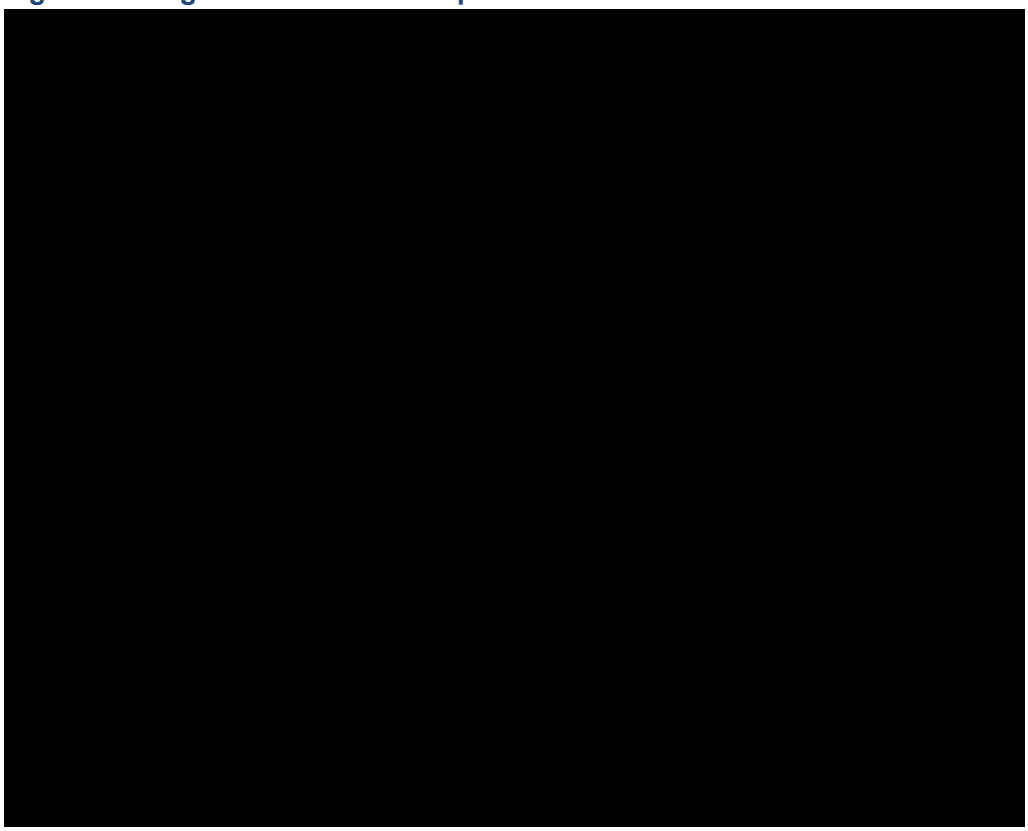
Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Progression-free survival

Contrary to the result of the significance test for PFS, the smoothed curve (Figure 23, subfigure C) depicts a violation of proportional hazards due to its 'U' shape. As the Cox model evaluates the mean slope of this curve, the test for significance in this case can be misleading. The proportionality of hazards for VenG and GClb was further explored by visual inspection of the log

cumulative hazards plot (Figure 24). The figure clearly depicts the curves for VenG and GClb crossing, leading to a divergence in the curves. Therefore, the assumption of proportional hazards between the treatments could not be accepted for PFS and an independent model was preferred as the base case.

Figure 24: Log cumulative hazard plots for PFS for VenG and GClb



Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Overall survival

For OS, the non-significant proportional hazards test is supported by the Schoenfeld residuals plot where the smoothed hazards curve is a straight line. Additionally, a closer inspection of the cumulative hazard plots (Figure 25) for VenG and GClb indicated that the curves cross two times. However, this occurs at timepoints with few events and no specific trend is observed over time. Overall, this demonstrates that there is little evidence to support a treatment effect on OS. Thus, for OS, the proportional hazards assumption between treatments was accepted and a dependent model was preferred as the base case. It should be taken into consideration that the data from both treatment arms are immature, therefore these results were further validated with clinical experts firstly at an AbbVie-organised HTA advisory board and also independently with clinical and health economic experts who validated the results of the OS curve generated from the dependent model. Experts also validated the approach of using the same CLL14 OS curve for both arms, on the basis that post-progression survival following initial treatment is now expected to be similar due to the availability of innovative subsequent treatments (venetoclax with rituximab [VenR] and ibrutinib) which have a greater impact on OS. It was also flagged that

CLL14 is an elderly and comorbid population, therefore in the long run patients from both arms are equally likely to die from other causes. Considering all of these points, it was considered reasonable to assume that first-line treatment does not have an effect on OS and the same survival extrapolation (from the GClb arm of the CLL14 trial) was applied to both arms when modelling the long-term OS benefits.

Figure 25: Log cumulative hazard plot for OS for VenG and GClb

Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up).
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

The full results of testing the proportional hazards assumption for TTNT are presented in Appendix M, where it was concluded that the assumption of proportional hazards could not be accepted. This result is expected given the close correlation, by definition, of TTNT to PFS in the first-line CLL setting. Moreover, the clinical expectation is that TTNT is expected to differ systematically between arms as a result of each regimen's benefit in delaying the need for subsequent treatment. Considering all these reasons, the individual model was selected for the base case.

Exploring proportional hazards assumption for del(17p)/*TP53* mutation population

Due to a small sample size of patients with the del(17p)/*TP53* mutation, the internal validity of modelling this population separately may be questionable. Thus, the predictive power of the available data was maximised by including del(17p)/*TP53* as a covariate when conducting the time-to-event modelling. This approach provided an estimated coefficient of how del(17p)/*TP53* status impacts the scale of the OS and PFS survival curves, thus having an impact on efficacy outcomes.

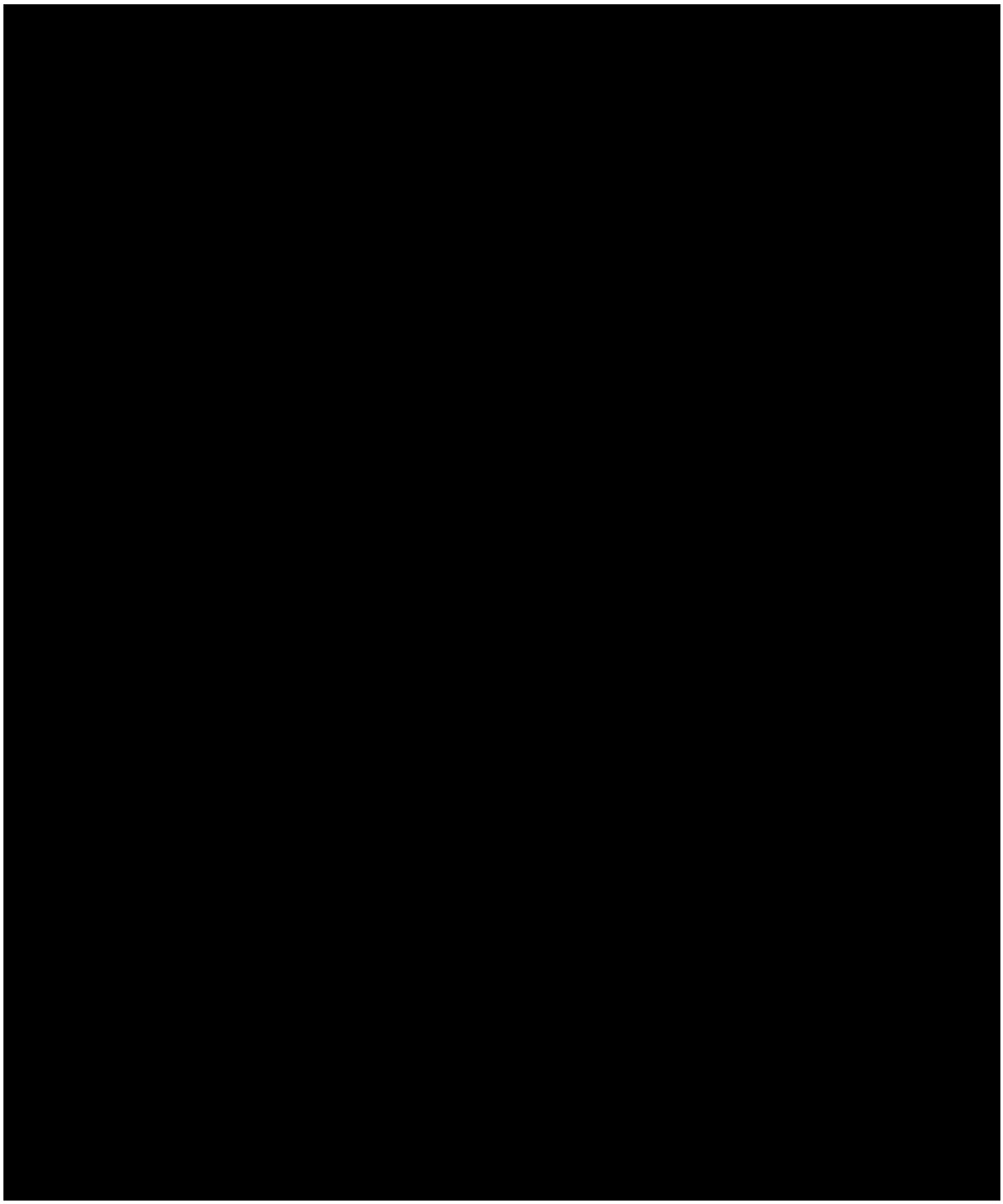
Of the patient level data analysed (n=432), a total of 31 patients (7.2% of total trial ITT population, see Section B.3.2.1) were categorised as having a del(17p)/*TP53* mutated karyotype.

Figure 26 (subfigure A and B) presents the Kaplan–Meier curves for OS and PFS stratified by treatment arm and del(17p)/*TP53* mutation status. As anticipated, patients with a positive mutation status have poorer OS and PFS outcomes in both treatment arms. Since the covariate approach assumes proportionality of hazards for the endpoints between the two groups per treatment arm, the proportional hazards assumption between the del(17p)/*TP53* mutation and non-del(17p)/*TP53* mutation populations was assessed. The scaled Schoenfeld residuals are presented in Figure 26 (subfigure D). The test results in a p value greater than 0.05 and the assumption of proportional hazards between the two populations holds for both outcomes (p value for OS=0.136 and PFS=0.099). It should be noted that since the sample size for this population is small, the results should be interpreted with caution, as the significance test is underpowered. Nonetheless, the visual inspection for this population implies that the proportional hazards assumption holds.

The log cumulative hazard plots for OS and PFS for the del(17p)/*TP53* mutation population are presented in Appendix M.

The full results of testing the proportional hazards assumption for TTNT in the del(17p)/*TP53* mutation population are presented in Appendix M, where it was concluded that the assumption of proportional hazards could not be rejected.

Figure 26: Kaplan–Meier curves for OS and PFS stratified by treatment arm and del(17p)/*TP53* mutation status, and assessment of proportional hazards assumption for OS and PFS



Source: CLL14 trial (August 2018 data cut: 28.1 months follow-up)
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

B.3.3.4 Survival analyses

The parametrisation of VenG and GClb time-to-event endpoints for the individual and dependent model were performed by fitting the available data from the CLL14 trial using maximum likelihood estimation. Independent review committee assessed endpoints were analysed.

The individual and dependent models were fitted to the following distributions: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised-gamma.

Additionally, spline 1–3 knot models based on the hazards, odds and probit (or normal) scale were also fitted to the observed time-to-event data. The spline models were applied using the *flexsurvspline* available in the *flexsurv* package in R. The underlying methodology for the application of spline models and the selection of corresponding knots is based on that outlined by Royston and Parmar.[92] These extrapolations are presented in Appendix M. The goodness of fit for the models were estimated based on model fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual fit following the recommendations in the NICE DSU Technical Support Document 14, and clinical plausibility of the long-term extrapolations.[91]

Both the AIC and BIC assess goodness of fit using a loglikelihood function. While the AIC penalises models only for additional and potentially inefficient parameters, the BIC also considers the sample size (number of observations). Lower AIC and BIC values indicate a better statistical fit.

$$AIC = -2 \times loglikelihood + 2 \times number\ of\ estimated\ parameters$$

$$BIC = -2 \times loglikelihood + ln(number\ of\ observations) \times (number\ of\ estimated\ parameters)$$

To assess the clinical plausibility and external validity, the landmark survival values were discussed with clinical experts and cross-validated with external sources (see Sections B.3.3.5–B.3.3.8 for more details).

B.3.3.5 Progression-free survival

Base case: *Independent model, log-logistic distribution*

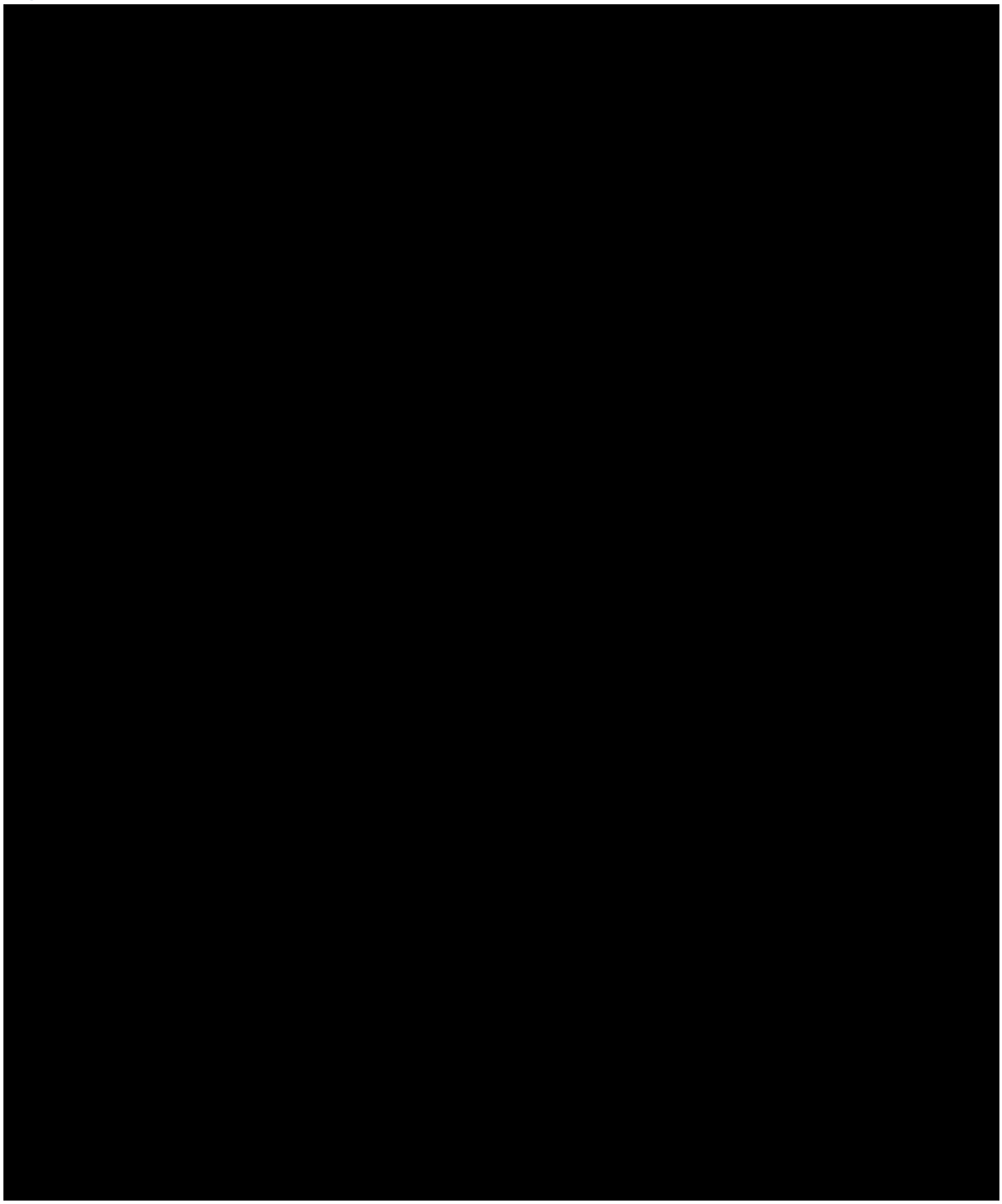
The observed data were parameterised individually per treatment without assuming proportionality in hazards between VenG and GClb, for PFS. However, the inclusion of the covariate del(17p)/*TP53* mutation (named del in the specification) allowed for the scale parameter to be varied in the estimation of PFS.

$$S(t) = del$$

The covariate (del) was applied to standard parametric distributions on the scale or rate parameter and was parametrised with an accelerated failure time interpretation (Weibull, log-logistic, log-normal and generalised gamma) or a proportional hazards interpretation (exponential and Gompertz). In this case, covariate effects were not interpreted on the hazard scale, but on the time/survival scale. Therefore, the covariate influenced the time it takes to reach some arbitrary level of cumulative hazard (i.e. time moves slower or quicker towards the endpoint considered).

Figure 27 provides the extrapolations for PFS for VenG and GClb over a 30-year (lifetime) time horizon, and Table 35 provides the model fit statistics (AIC and BIC). The exponential model provided the best statistical fit for the VenG extrapolations and the log-logistic model provided the best statistical fit for the GClb extrapolations. Projections were also discussed with experts and the log-logistic was validated as the extrapolation that is closest to what is seen in clinical practice for GClb. Following the advice from the NICE DSU technical support document (TSD) 14 to use the same curve between arms,[91] it was decided that the log-logistic model was the most accurate prediction when compared to the observed, more mature data from CLL11 and with a reasonable fit to the CLL14 Kaplan–Meier PFS data. Experts also validated that predictions from the independent (log-logistic) model were clinically plausible, therefore it was decided that this would better represent the data and observed relative difference between arms in terms of PFS benefit.

Figure 27: Parametric extrapolations for PFS for VenG and GClb (independent model)



Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Table 35: Model fit statistics (AIC and BIC) for the individual model extrapolations for PFS (independent model)

Distribution	AIC		BIC	
	VenG	GClb	VenG	GClb
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Table 36 presents the 5-, 10-, 20- and 30-year landmark survival estimates from the individual modelling of PFS. Due to immature data for VenG and GClb, there was a large degree of variability in the predicted PFS over 20 years. While the exponential distribution provided the most appropriate statistical model fit for VenG, the violation of the proportional hazard assumption deemed this distribution inappropriate to be used as the base case. Additionally, as also validated by a health-economics expert, only distributions with differences in AIC or BIC that exceed four should be considered meaningful when assessing distribution choice. Therefore, external data with longer term follow-up was used to inform the selection of the base case extrapolation curves. The most appropriate source of evidence that is closest to the CLL14 trial population is the CLL11 trial as it provides longer-term follow up data for GClb, reporting a 5-year PFS of 23%.[86] Table 36 shows that, for the GClb arm, the log-logistic (27.65% at 5 years), and generalised gamma (27.16% at 5 years) distributions most closely align with long-term follow-up data from the CLL11 trial. Next, the log-logistic distribution was selected as it provided a good fit to the data (Table 36) and based on exploration of the hazard functions (see Appendix M). Finally, the projections were discussed with UK clinical experts and the log-logistic was validated as the one that is closest to what is seen in clinical practice for GClb.

Table 36: Landmark survival for the individual model for PFS (independent model)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

It was also advised by statistical experts that clinical opinion should supersede statistical fit in instances where data are immature. Given the immaturity of observed data from CLL14, this also led to the conclusion that the log-logistic was the most optimal distribution and should be selected as base case.

In conclusion, based on goodness of fit assessment, validation with external sources and UK clinical expert advice, the log-logistic model was found to provide the most plausible long-term PFS estimates for GClb. Considering the larger degree of uncertainty surrounding the long-term PFS estimates for VenG compared to GClb, to ensure the same distribution is used for both independent models, despite the exponential distribution showing a better fit to the data, the log-logistic distribution was used as the base case for both arms.

Scenario: *Dependent model, Weibull distribution*

An alternative scenario, exploring a dependent model for PFS is presented in Appendix M. This was not used as the base case as the proportional hazard assumption does not hold in this case (see Section B.3.3.3).

B.3.3.6 Overall survival (all cause death)

Base case: *Dependent model, exponential distribution*

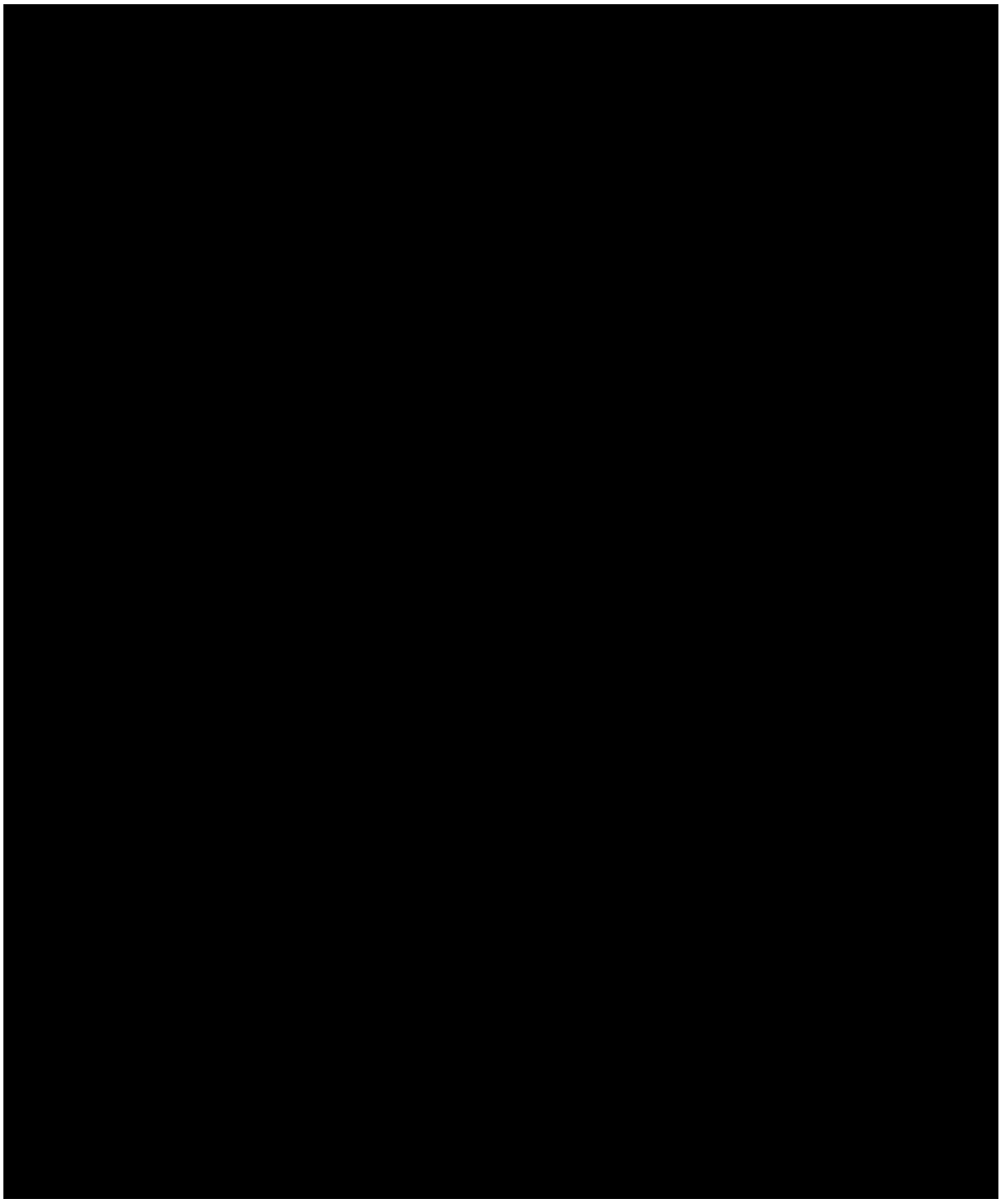
The dependent model was fitted to OS separately and included treatment as a covariate (named *tx* in the specification). The model also incorporated the differential effect of del(17p)/*TP53* mutation on the endpoints (named *del* in the specification).

$$S(t) = del + tx$$

Figure 28 presents the estimated OS extrapolations for VenG and GClb over a 30-year time horizon. A visual inspection of the long-term extrapolations for the dependent model (Figure 28) and the extrapolations for the individual model (Appendix M) indicated that the dependent model including del(17p) mutation as a covariate showed less volatility in the estimation of OS over the long term, and as described in Section B.3.3.3, the proportional hazards assumption was held for the dependent model.

While the AIC depicted that the log-normal model provided a good fit to the observed data (Table 37), the BIC penalised this model for additional parameters and indicated that the exponential model with constant hazards provided the best statistical fit, followed by the log-normal model. However, due to the unrealistic nature of the hazards (presented in Appendix M) for the log-normal model (decreasing over time), it was not suitable to choose this as the base case for the economic model.

Figure 28: Parametric extrapolations for OS for VenG and GClb (dependent model)



Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; OS: overall survival; VenG: venetoclax with obinutuzumab.

Table 37: Model fit statistics (AIC and BIC) for the individual model extrapolations for OS (dependent model)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; OS: overall survival.

Long-term OS estimates from Brenner et al.[93] indicate that the absolute survival over 10 years in the previously untreated CLL population in the US was between 28–35%, and relative survival estimates (compared with survival of the general population) ranged between 46–55%. More recent studies by Pulte et al.[94] and Bista et al.[95] indicate the relative OS estimates for 10 years correspond to between 51–64%. Shvidel et al. (2011)[96] estimated the actuarial long-term survival at 53% over 10 years, and 25% over 20 years.

The 5-, 10-, 20- and 30-year survival estimates for CLL14 derived using the dependent modelling approach are presented in Table 38. The long-term survival estimates modelled are closer to the relative survival estimates based on real world data instead of the absolute long-term survival. However, this can be explained by the fact that these sources are using data from a treatment era where efficacious treatment options, particularly treatments for relapsed or refractory (R/R) CLL such as BCRis were lacking. To explore the impact of relaxing the proportional hazards assumption, individual modelling was also explored and presented in Appendix M although those analyses were not considered suitable for the model's base case. Based on the CLL14 trial evidence, UK clinical experts expect VenG to extend PFS to a larger extent than GClb, however, once patients relapse, innovative R/R therapies would be a key driver of OS from relapse to death. In other words, any difference in OS between first-line treatments that would have been observed in a world without R/R treatments is obfuscated by the availability of innovative second-line CLL treatments. Thus, time in the progression free state best captures any differential effect between first-line treatments. This rationale also helped to shape the decision to select the dependent model applying the same OS curve (Table 38) in both arms as a base case.

Table 38: Landmark survival for the dependent model for OS (without treatment effect) model)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

OS base case selection

After exploring a variety of approaches (including using data from the CLL11 trial to model OS), and after eliciting clinical expert opinion, it was determined that the source of evidence providing the most plausible OS estimates was the CLL14 trial. Expert validation of the landmark survival estimates determined that the dependent model using the exponential distribution was the most appropriate base case.

Clinical experts agreed that, pending longer follow-up data, it is reasonable to assume there would be no difference in OS between VenG and GClb since post-first relapse, these patients are salvaged quite quickly with innovative R/R CLL treatments. Based on this expert opinion, and in the absence of statistically significant OS data from the CLL14 trial, the treatment effect of VenG and GClb was assumed to be the same. This is a conservative approach; as discussed in section B.1.3.4, there is published evidence of a positive correlation between undetectable MRD and prolonged OS which would indicate an OS benefit in the VenG arm, when compared to GClb, could be anticipated due to the superior undetectable MRD results for VenG both on- and off-treatment.[23]

The CLL14 OS curve provided a good fit to the observed data and the predictions of long-term survival outcomes were considered to be plausible by clinical expert opinion. To further explore the validity of the CLL14 OS extrapolation with external sources, PPS estimates were generated using 1) 5-year follow-up data from the CLL11 trial, 2) the ibrutinib arm from the RESONATE trial, and 3) the ibrutinib arm generated using the Warwick Evidence Review Group (ERG) network meta-analysis (NMA) from NICE appraisal, TA561.[3, 86, 97] This resulted in the following observations:

1. The OS curves generated from the CLL11 data lie well below the (observed and extrapolated) CLL14 OS curve (see Figure 29). As discussed with UK clinical experts, this may be explained by the fact that CLL11 was undertaken before effective subsequent therapies (venetoclax monotherapy or ibrutinib) were available and/or because, as discussed in section B.3.2.3, in the CLL14 trial chlorambucil was given for six additional cycles compared to the CLL11 trial. Therefore, the CLL11 trial is not generalisable to the decision problem presented in this submission and is only presented as a scenario analysis for completeness.

Figure 29: Overall survival with CLL11 post-progression survival data

Note that the blue line for VenG is not visible as the same OS curve is applied to both trial arms of CLL14 (VenG and GClb [red]).
Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; Ven+G: venetoclax with obinutuzumab.

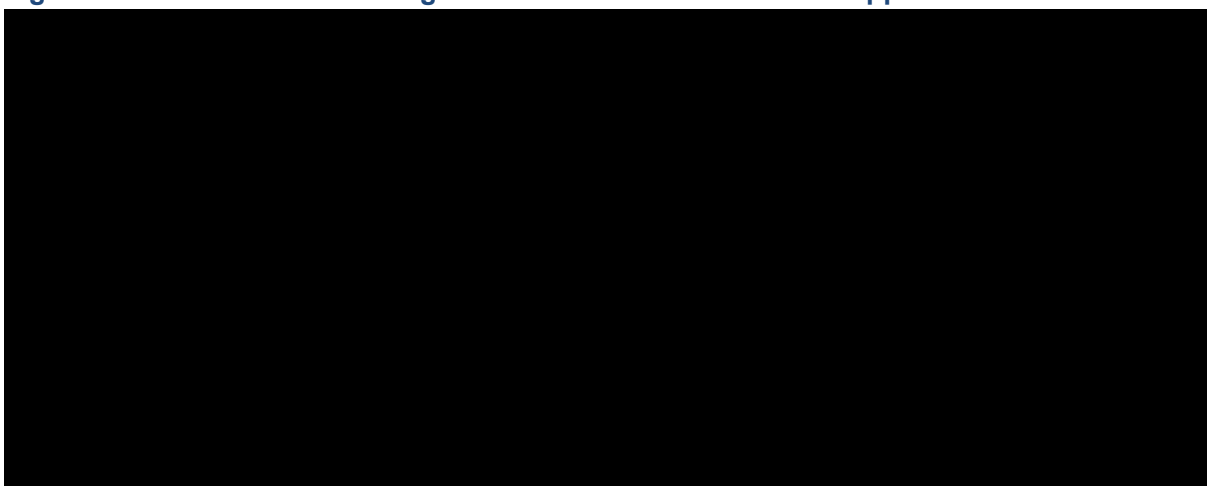
2. The OS curve generated from the application of the ibrutinib arm from the RESONATE trial lies well below the (observed and extrapolated) CLL14 OS curve (see Figure 30). However, the OS curve lies above the OS curve generated from the CLL11 data and is closer to the Kaplan–Meier curves than the CLL11 generated OS curve, although still not perfectly capturing the OS effect seen in CLL14 Kaplan–Meier data. It would be expected for the OS curve generated using the RESONATE data to lie below the observed and extrapolated CLL14 OS curve since nearly 30% of the RESONATE patient population consisted of del(17p) patients (ibrutinib arm: 59/195 had del[17p]) who have poorer outcomes compared to patients who do not have this genetic disposition.[97] Therefore results from this approach are only explored in scenario testing.

Figure 30: Overall survival using RESONATE trial ibrutinib arm

Note that the blue line for VenG is not visible as the same OS curve is applied to both trial arms of CLL14 (VenG and GClb [red]).
Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; Ven+G: venetoclax with obinutuzumab.

3. The OS curve generated following application of the ibrutinib arm from Warwick ERG's NMA in relapsing CLL for TA561 lies above the OS curve for the CLL14 patient population but is relatively close to CLL14 PPS data (see Figure 31 and Table 39). Therefore, although this approach cannot be used as a base case it can be as a benchmark on how CLL14 extrapolations compare to other sources of data and approaches that factor in impact of innovative treatments.

Figure 31: Overall survival using Warwick ERG NMA from NICE appraisal TA561



In this scenario, the OS projection curves are higher than general population mortality, and so background mortality is modelled instead.
Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; Ven+G: venetoclax with obinutuzumab.

Table 39 provides an overview of the resulting PPS life years (LY) generated in the first-line CLL model as part of the validation exercise when using external data sources.

Table 39: PPS (LYs) following application of external data

	PPS (LYs) after application of external data	CLL14 PPS (LYs)
CLL11 (GClb arm)	4.85	10.12
RESONATE (ibrutinib arm)	7.92	
Warwick ERG NMA, TA561 (ibrutinib arm)	10.28	

Abbreviations: ERG: Evidence Review Group; GClb: chlorambucil with obinutuzumab; LYs: life-years; NMA: network meta-analysis; PPS: post-progression survival.

Scenario: *Independent models*

An alternative scenario, exploring independent models for OS is presented in Appendix M. This was not used as the base case as the proportional hazard assumption was not rejected for OS and also because no treatment effect is assumed for OS, as per expert validation (see Section B.3.3.3).

B.3.3.7 Time-to-next treatment

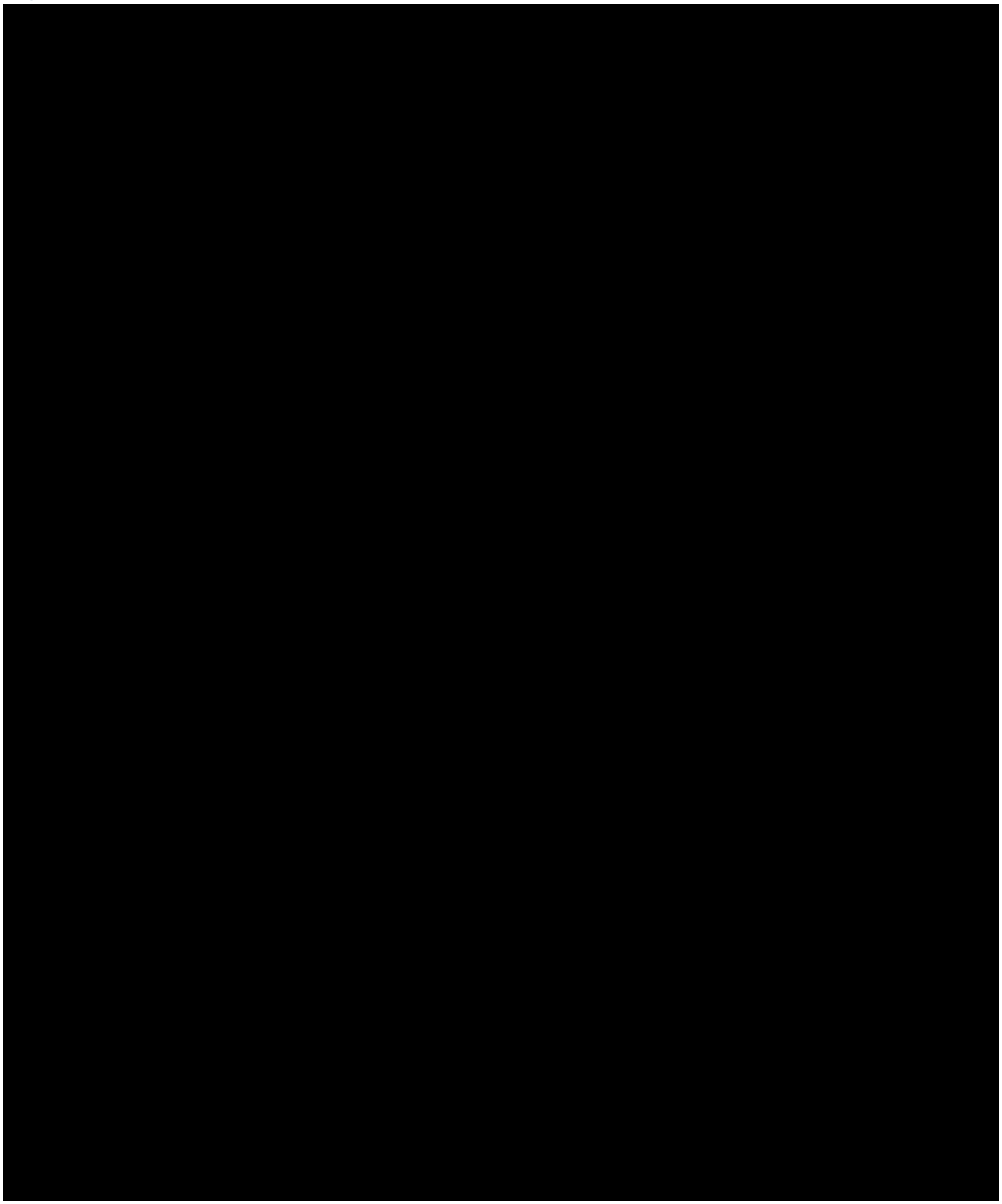
Base case: *Independent model, Weibull distribution*

TTNT information from CLL14 is used to estimate when costs of subsequent treatments will occur after patients have progressed. For the independent model, the observed data were parametrised individually per treatment without assuming proportionality between VenG and GClb. However, as del(17p)/*TP53* mutation is an important driver of treatment outcomes, the inclusion of the covariate del(17p)/*TP53* mutation (named del in the specification) allowed for the scale parameter to be varied in the estimation of TTNT.

$$S(t) = del$$

Figure 32 provides the extrapolations for TTNT for VenG and GClb over a 20-year time horizon. Table 40 provides the accompanying AIC and BIC for the models fit statistics. The exponential model provided the best statistical fit for VenG, while the Gompertz distribution provided the best statistical fit for the GClb extrapolations.

Figure 32: Parametric extrapolations for TTNT for VenG and GClb (individual model)



Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; PFS: progression-free survival; TTNT: time-to-next- treatment; VenG: venetoclax with obinutuzumab.

Table 40: Model fit statistics (AIC and BIC) for the individual model extrapolations for TTNT (independent model)

Distribution	AIC		BIC	
	VenG	GClb	VenG	GClb
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
1-knot hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]
3-knot hazard	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]	[redacted]	[redacted]

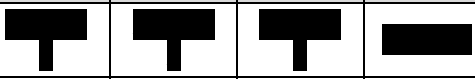
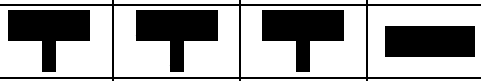
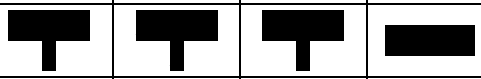
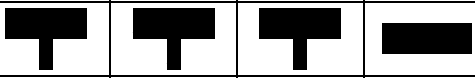
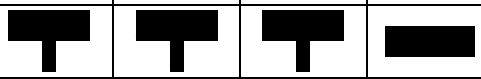
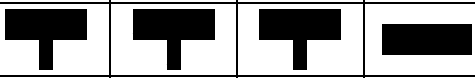
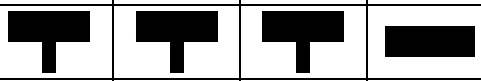
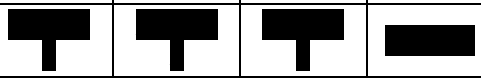
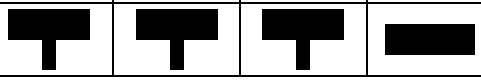
The spline 1-knot and 2-knot models on the 'normal' scale were not optimised (no solution found) and are thus not presented

Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

The extrapolations for TTNT were associated with a large degree of uncertainty. Therefore, the CLL11 trial was used as an external source of evidence to validate the extrapolation results in the trial, as it considered the same treatment (GClb) and patient population (previously untreated CLL with coexisting comorbidities). Survival analysis from the CLL11 trial reports that at 5 years 49% (95% CI: 42, 55) of patients had not experienced a next treatment event.[86] Table 41 shows that the exponential (68.01%) and log-normal (66.81%) distributions overestimate 5 year TTNT projections relative to the CLL11 trial data and the Gompertz distribution underestimates it in the long-run with a steep decrease to 1.21% at 10 years onwards, leaving the Weibull, log-logistic and spline models as potential candidates for the base case taking into account best statistical fit and comparison to observed data.

Table 41: Landmark survival for the individual model for TTNT (independent model)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
1-knot hazard								
1-knot odds								
1-knot normal								
2-knot hazard								
2-knot odds								
2-knot normal								
3-knot hazard								
3-knot odds								
3-knot normal								

Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

Subsequently, the hazard functions for these distributions were explored (Appendix M). The log-logistic distribution resulted in decreasing hazards over time, which is clinically implausible, since TTNT is associated with disease progression.

Having ruled out a number of distributions, the statistical fit was assessed, and it was observed from Table 40 that the Weibull distribution provided a superior fit when compared to the generalised gamma distribution and spline models for GClb. This was also observed for the VenG extrapolations. Given that the Weibull distribution provided a good statistical fit and compared well against observed data, this distribution was used as the base case for both arms as per the advice from NICE DSU TSD 14.[91]

B.3.3.8 Time on treatment (ToT)

ToT parameter is used to calculate medication costs according to the average time on treatment as per the observed data from CLL14. ToT for VenG and GClb arms were protocol-driven and the fixed treatment durations observed from the Kaplan–Meier curves were used to inform the ToT curves in the model. Extrapolations of the ToT were not conducted or implemented in the model as no patient was on treatment beyond the fixed treatment duration period stated within the protocol.

ToT was estimated based on discontinuation of therapy using censoring pegged to OS. Patients who received a dose of venetoclax in the VenG arm, and those who received a dose of chlorambucil in the GClb arm were included in these analyses. Treatment discontinuation for a total of 203 patients in the VenG arm and 212 patients in the GClb arm was analysed. The observed Kaplan–Meier data for discontinuation of therapy are presented in Figure 33, and were used to model time on treatment in the economic model.

The median ToT before discontinuation was achieved at [redacted] days (mean [redacted] days) for VenG versus [redacted] days (mean [redacted] days) for GClb.

For the comparison with ibrutinib in the del(17p)/*TP53* population, the recommended treatment duration determined the time on treatment. The PFS curves for ibrutinib determined the patient distribution of the number of patients who are on treatment.

Figure 33: Kaplan–Meier curves for ToT for VenG and GClb

Abbreviations: GClb: chlorambucil with obinutuzumab; ToT: time on treatment; VenG: venetoclax with obinutuzumab.

B.3.3.9 PFS and OS for ibrutinib (del(17p)/*TP53* population)

The relative treatment efficacy of ibrutinib versus VenG in terms of PFS and OS hazard ratios were estimated from a naïve comparison. The clinical review from the SLR identified the sources used for the comparison to ibrutinib monotherapy data, and the results were presented in Section B.2.9.

In the CLL14 trial, there were 24 patients in the VenG arm with del(17p)/*TP53* mutation status. Kaplan–Meier curves from this CLL14 VenG subgroup were naïvely compared to those provided by the ibrutinib source for the same timeframe, or longer. This was done to ensure consistency between information from CLL14 and published literature (i.e. patients with *TP53* aberrations). Information from the curves on the numbers of patients at risk were used to calculate a HR

comparing patients with del(17p)/*TP53* mutation on VenG in the CLL14 trial with patients with del(17p)/*TP53* mutation in the ibrutinib studies.

The PFS hazard ratio from the naïve comparison was combined with the VenG PFS curve (Figure 53) for those patients with the del(17p) mutation (n=17) to generate the individual ibrutinib PFS curve. Similarly, the OS hazard ratio from the naïve comparison was combined with the VenG OS curve (Figure 53) to generate the individual OS curve for those patients with positive del(17p) mutation status.

Figure 34 PFS and OS Kaplan–Meier curves from CLL14 for VenG arm

Abbreviations: OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Two key sources of evidence were detected by the clinical SLR: Mato et al. 2018 and Ahn et al. 2016; Ahn et al. 2016 was a longer follow-up of the data from Farooqui et al. 2014 presented by the manufacturer in the NICE appraisal for ibrutinib in CLL (NICE TA429), but which was not accepted for decision making.[34, 60, 71, 72]

As discussed in Section B.1.3.4, ibrutinib was recommended in this indication, despite the absence of randomised trial data because of the high unmet need in previously untreated CLL patients with del(17p)/*TP53* mutation. In the absence of data, a simplifying assumption was made during the NICE appraisal that the treatment effect in the relapsed/refractory del(17p)/*TP53* population could be generalised to the previously untreated del(17p)/*TP53* population.[34, 55] The NICE appraisal committee recognised that this simplifying assumption was associated with uncertainty.

Table 42 shows the results of the naïve comparisons using both sources of evidence, with the extrapolated PFS and OS curves utilised in the model shown in Figure 35 and Figure 36, respectively. Caution should be applied when interpreting these figures since the data used in

the analyses were retrieved from single arm studies. In addition, the naïve comparison method was selected since adjustment for prognostic factors was not feasible due to the limited information on patient characteristics available in the publications. Results from these analyses are driven by small sample sizes, creating a high level of uncertainty in the estimation of benefit differences between VenG and ibrutinib, as reflected by the broad confidence intervals and lack of statistical significance.

Table 42: PFS and OS Hazard ratios for del(17p)/*TP53* mutation population using naïve comparisons

HR: Ibrutinib vs VenG	PFS		OS	
	Mato et al.[60]	Ahn et al.[71]	Mato et al.[60]	Ahn et al.[71]
Mean HR	[redacted]	[redacted]	[redacted]	[redacted]
Standard error	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
p value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 35: PFS curves utilised in model for VenG and ibrutinib for del(17p)/*TP53* mutation population

[redacted]

Abbreviations: Ibr: ibrutinib; KM: Kaplan-Meier; PFS: progression-free survival; Ven+G: venetoclax with obinutuzumab.

Figure 36: OS curves utilised in model for VenG and ibrutinib for del(17p)/*TP53* mutation population

Abbreviations: Ibr: ibrutinib; KM: Kaplan-Meier; OS: overall survival; Ven+G: venetoclax with obinutuzumab.

B.3.3.10 Background mortality

The latest UK life tables published by the Office for National Statistics (ONS, 2015-2017) were used to estimate the background mortality (i.e., the general population mortality).[98] To match the CLL14 trial population, age and gender adjustments were applied. Background mortality was applied to ensure that the hazards of PFS, OS and TTNT are either always equal to or greater than the background mortality hazards. Constraining the OS, PFS and TTNT hazard rates to the background mortality hazard rate ensures that any flat tails of the parametric survival models do not lead to implausible long-term survival outcomes.

The extrapolated OS based on the CLL14 trial (both the VenG and GClb arms) are close to the general population mortality curves generated from UK life tables (Section B.2.6.5). Clinical experts were consulted to judge if this were reasonable and confirmed that as a result of the age profile (median age of patients was 72 years) and comorbid nature of the CLL14 trial population, patients would be increasingly likely to die from non-CLL causes, the longer they live. Furthermore, due to recent innovation in treatment for R/R CLL (venetoclax with rituximab; ibrutinib), patients have treatments that can limit the impact of CLL but do not reduce the risk of non-CLL causes of death. The extrapolated OS based on the CLL14 trial appears to support this trend. For the VenG arm, patients live in the progression-free state for longer (PFS = [redacted] years in the base case calculation) and as they get older, their comorbidities take more prominence and increase the probability of dying from other causes, thus they either die before progressing or soon after progressing. For the GClb arm, patients spend less time in the PFS state (PFS = [redacted] years in the base case calculation), they live in the progressed state for much longer, as a result of the innovative R/R treatments, which limit the impact of CLL, leaving them exposed to other causes of death.

In conclusion, the extrapolated OS based on the CLL14 trial, as validated by clinical experts was used in the base case. Nevertheless, a scenario is presented whereby an additional risk of dying (e.g. due to infections or secondary cancers) is included for CLL patients. This is assumed to be

an additional risk of death of 10–15%, based on clinical expert suggestions and long-term follow-up data of untreated CLL patients (19% additional risk of dying).[36]

B.3.3.11 Base case survival extrapolations summary

PFS (vs GClb in non-del(17p)/*TP53*): As concluded in Section B.3.3.5, the log-logistic model was found to provide the most plausible long-term PFS estimates for GClb based on goodness of fit assessment, validation with external sources and UK clinical expert advice. Thus, the log-logistic model was applied to VenG and GClb in the base case.

PFS (vs ibrutinib in del(17p)/*TP53*): As discussed in Section B.3.3.9, the naïve comparison to Mato et al. estimated an HR of [redacted](95% CI: [redacted], p=[redacted]), albeit it is not statistically significant with wide confidence intervals, which is reflective of the very small sample sizes of the available data. Thus, no conclusions can be made about the relative PFS of ibrutinib vs VenG. It should also be noted that it was not feasible to adjust for between trial differences and this renders point estimates to further uncertainty. This HR was used in the base case extrapolations

OS (vs GClb in non-del(17p)/*TP53*): As discussed in Section B.3.3.6, OS data in CLL14 are immature, driven by only a few events and are not statistically significant. UK clinical experts at an AbbVie-organised advisory board confirmed no conclusions could be drawn from the CLL14 OS data and that in the absence of data, it was reasonable to assume an HR of 1 (i.e. no difference in OS between VenG and GClb). It was further validated, that innovative treatments for R/R CLL patients are likely to obfuscate any OS difference between first-line treatments that might have occurred in a world without these innovative R/R treatments. Clinical experts also confirmed that this is a conservative approach, since in the CLL14 trial, the CR rates and undetectable MRD levels were significantly much higher in the VenG arm than the GClb arm, which would normally translate to a better long-term OS. The exponential distribution was selected for both arms in the base case as it provided the best visual fit (Section B.3.3.6) when compared to the CLL14 observed data.

OS (vs ibrutinib in del(17p)/*TP53*): The naïve comparison to Mato et al. estimated an HR of [redacted](95% CI: [redacted]; p=[redacted]).[60] Similar to the PFS results, the OS results were not statistically significant and have wide confidence intervals, which is reflective of the very small sample sizes of the available data. Thus, no conclusions could be made about the relative OS of ibrutinib vs VenG. This HR was used in the base case extrapolations. Additional scenario analyses were performed using a different data source from the literature (Ahn et al.[71]), but the small sample size also meant that no conclusions could be drawn. Finally, in line with the approach taken in the VenR NICE appraisal, a scenario assuming equal efficacy between VenG and ibrutinib was also explored as an aid to decision making.[3]

TTNT: The Weibull model was selected as the base case for both (VenG and GClb) arms as it was considered the best statistical fit and the GClb extrapolations aligned with observed data from CLL11.

External validation (CLL11 GClb arm vs CLL14 GClb arm): All extrapolations were externally validated using the CLL11 trial, and differences in landmark results (See Table 43) between the CLL11 GClb arm and the CLL14 GClb arm may be partly explained by innovation in treatments

for R/R CLL following the CLL11 trial and the difference in the number of cycles of chlorambucil used.

Table 43: Five-year landmark survival comparison between CLL11 and CLL14

	GClb CLL11 Kaplan–Meier data	GClb CLL14 Extrapolation	Model used for extrapolation for CLL14
PFS: 5-year	24.35%	[redacted]	Log-logistic, independent model
OS: 5-year	66.7%	[redacted]	Exponential, dependent model
TTNT: 5-year	49.65%	[redacted]	Weibull, independent model

Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

Table 42 provides an overview of the base case distribution choices for each outcome, per treatment arm and population.

Table 44: Overview of base case distribution choices

Endpoint	Non-del(17p)/*TP53*	Del(17p)/*TP53*
PFS	VenG: Independent model, log-logistic GClb: Independent model, log-logistic	VenG: Independent model, log-logistic Ibrutinib: Mato HR
OS	Dependent model, exponential distribution No treatment effect assumed	VenG: Dependent model, exponential distribution Ibrutinib: Mato HR
TTNT	VenG: Independent model, Weibull GClb: Independent model, Weibull	VenG: Independent model, Weibull Ibrutinib: Incident patients who have progressed and not died
ToT	Non-del(17p) ToT curves per treatment arm from CLL14 trial	VenG: Del(17p) ToT curve for VenG from CLL14 trial Ibrutinib: PFS curve for ibrutinib

Abbreviations: GClb: chlorambucil with obinutuzumab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; ToT: time-on-treatment; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

B.3.3.12 Adverse event probabilities

Adverse events were chosen according to those that are treatment emergent and of grade 3/4 in severity, which had an incidence of ≥1% in the key trial arms for each included treatment. Adverse events are assumed to occur within the first cycle of the model, a simplification which is used in numerous cancer models.[99, 100] Hence, only the adverse events of the direct comparators GClb and ibrutinib are considered in the model, and not for any subsequent treatments. Adverse events are associated with one-off costs and negative HRQoL impacts. Table 45 provides the overview of the probabilities alongside the sources used to inform the table.

Table 45: Adverse event probabilities utilised in cost-effectiveness model

AE incidence	VenG	GClb	Ibrutinib
Asthenia	2.40%	0.50%	0.00%
Diarrhoea	4.20%	0.50%	4.00%
Dyspnoea	2.40%	0.50%	0.00%
Febrile neutropenia	5.20%	3.70%	1.00%

Infusion related reaction	9.00%	9.80%	0.00%
Leukopenia	2.40%	4.70%	0.00%
Neutropenia	52.80%	48.10%	12.00%
Pneumonia	4.20%	4.20%	0.00%
Sepsis	3.30%	0.90%	0.00%
Thrombocytopenia	13.70%	15.00%	0.00%
Source	CLL14[70]	CLL14[70]	Barr 2018[101]
N (Sample size)	212	214	136

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

Utility analysis using EQ-5D-3L data from the CLL14 trial (see Section B.2.6.9) was performed by fitting linear mixed effects models for repeated measures. The statistical models included utility score as a dependent variable. To determine the relevant covariates, different regression models were implemented by including an additional independent variable at time. The covariates included in the models were age, sex, treatment arm and time, to account for assessment point. By adding a covariate at time, six different models were fitted. The "lmer" function from the lme4 package in R was used to estimate the models.

After determining the level of significance and the magnitude of each estimated coefficient, the models that best predict the utility values from the CLL14 trial were determined to be as follows, labelled model 1 and model 2, where time is included as a relevant variable.

- Model 1: $U_{it} = \alpha + \beta_1 txarm_i + \beta_2 age_i + \beta_3 sex_i + \varepsilon_{it}$
- Model 2: $U_{it} = \alpha + \beta_1 txarm_i + \beta_2 age_i + \beta_3 sex_i + \beta_4 cycle_t + \varepsilon_{it}$

Where the term U_{it} denotes the utility value (EQ-5D index score) measured for patient *i* at time *t* and ε_{it} is the residual random error for patient *i* at time *t*.

The PFS utility value could be estimated from either model 1 or 2 and a summary of the values identified that can be used for the overall population and the individual populations is presented in Table 46.

Table 46: Summary of estimated PFS utility values from CLL14

	Overall population	Del(17p)/*TP53*	Non-del(17p)/*TP53*
Model 1	[redacted]	[redacted]	[redacted]
Model 2 (with time)	[redacted]	[redacted]	[redacted]

Abbreviations: PFS: progression-free survival.

The PFS utility values from CLL14 that could be used for the overall population and the non-del(17p)/*TP53* population are those estimated from model 2, which considers time as a relevant variable and thus is more in line with the progressive nature of this disease. For the

del(17p)/*TP53* population, the PFS utility value that could be used is that estimated from model 1, as time is not a significant variable for this population.

These data were presented to clinical and health economic experts at an AbbVie-organised advisory board, where it was determined that the utility estimates were infeasibly high for the previously untreated CLL population as they exceed those of the age-matched general population (70-year old female 0.77, male 0.79).[102] It was advised that values for the PFS and PPS period from the most recently published data sources should be used instead, as presented in Section B.3.4.5.

B.3.4.2 Mapping

No mapping methods have been implemented as part of this submission.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted in December 2018 and updated in July 2019 to identify studies assessing the health-related quality of life of patients with previously untreated CLL. The SLR identified 16 studies reporting relevant health-related quality of life data. Full details of the methods and results can be found in Appendix H. A summary of the health-related quality-of-life studies included in the SLR are presented in Appendix H.

None of the identified health-related quality-of-life studies elicited utility values from a UK population using EQ-5D, and therefore were not in line with the NICE reference case. As a result, an alternative source of utility values for the previously untreated CLL economic model were sought. While the CLL14 trial utilised the EQ-5D to elicit utility data, clinical and health economic experts at an AbbVie-organised advisory board considered that the utility estimates were notably higher than those accepted in previous appraisals and published UK age-adjusted general population values. The utility values from TA343 were instead used because these have previously been accepted as plausible by NICE to best represent the population of this decision problem (please see Section B.3.4.5).[67]

B.3.4.4 Adverse reactions

Adverse event disutility values and duration estimates are used to assess the impact of adverse events on QALYs. The disutility value per adverse event are multiplied with the duration of the adverse event to reach a quality-adjusted life year (QALY) decrement. During the first model cycle the QALY decrement is applied. The parameters for each adverse event have been sourced from previous NICE technology appraisals and published literature (see Table 47).

Table 47: Adverse event QALY decrement inputs

AE	Disutility (positive)	SE	Duration (days)	SE	QALY decrement	Reference
Asthenia	0.115	0.012	35.35	3.54	0.011	NICE appraisal TA306;[103] Lloyd et al. 2006;[104] PIX301 trial
Diarrhoea	0.080	0.008	3.50	0.35	0.001	NICE appraisal TA216;[66] Beusterien 2010;[105] NICE appraisal TA344[68]
Dyspnoea	0.103	0.010	21.7	2.10	0.004	NICE appraisal TA306; [103] Lloyd et al. 2006; [104] PIX301 trial
Febrile neutropenia	0.150	0.015	3.50	0.35	0.001	Lloyd et al. 2006; [104] NICE appraisal TA344[68]
Infusion related reaction	0.200	0.020	3.50	0.35	0.002	NICE appraisal TA344[68]
Leukopenia	0.090	0.009	14.01	1.40	0.003	Assumed to be the same as neutropenia; PIX301 trial
Neutropenia	0.090	0.009	3.50	0.35	0.001	Nafees et al. 2008;[106] NICE appraisal TA344[68]
Pneumonia	0.195	0.020	18.21	1.82	0.010	Tolley et al. 2013;[107] NICE appraisal TA359[56]
Sepsis	0.195	0.020	7.00	0.70	0.004	Tolley et al. 2013; [107] UK NHS Adboard
Thrombo-cytopenia	0.108	0.011	23.21	2.32	0.007	Tolley et al. 2013; [107] NICE appraisal TA359[56]

Abbreviations: AE: adverse event; QALY: quality-adjusted life year; SE: standard error.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Following presentation of the utility analysis from CLL14 (shown in Section B.3.4.1) to clinical and health economic experts at an AbbVie-organised advisory board, it was considered that the utility estimates were notably higher than those accepted in previous appraisals and published UK age-adjusted general population values. Instead, it was advised that values for the PFS and PPS period from the most recently published data sources should be used. Utility values from the CLL14 trial are explored in scenario testing for completeness.

TA343 (GClb for untreated CLL) was used to inform the base case of the model, the results of which are presented in Table 48.

Table 48: Base case utilities utilised in the model

Progression stage	Utility value	Source	Rationale for use
Pre-progression	0.670	TA343: PFS under IV treatment	VenG and GClb include IV treatment. This is applied for the whole PFS state and is a conservative but simplifying approach.
Post-progression	0.600	TA343*: weighted average of the following utilities (progression after first-line treatment, PFS ± second-line treatment, relapsed line of treatment)	Used as base case and aligned with what has been accepted in previous NICE CLL appraisals.[34, 67]

*Utility for the population considered (patients unsuitable for FCR/BR) is calculated as a weighted average of patients suitable and unsuitable for FCR/BR
Abbreviations: BR: bendamustine with rituximab; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

The cost and resource use categories were aligned for consistency with the recent appraisal TA561 for VenR for relapsing/refractory CLL.[3] These cost categories were validated by five UK-based clinical experts at an AbbVie-organised advisory board, and small changes were made compared to TA561 based on their feedback.[3]

B.3.5.1 Intervention and comparators' costs and resource use

Active treatment costs

The British National Formulary (BNF) online database was used to source the drug costs for all the treatment regimes.[108] Table 49 is an overview of all the drugs included in the model along with the cost per pack size and the cost per mg of the drug. Table 50 presents the treatment regimens identified from the SLR.

Table 49: Drug costs for venetoclax and comparators

Drug	Dose per tablet or vial	Units per package	Cost per package	Price per mg	Source
Venetoclax Tablet, mg	10 mg	14	£59.87	£0.43	BNF: Venclyxto (AbbVie Ltd)
	50 mg	7	£149.67	£0.43	
	100 mg	7	£299.34	£0.43	
	100 mg	14	£598.68	£0.43	
	100 mg	112	£4,789.47	£0.43	
Obinutuzumab, IV, mg/ml	1000mg	1	£3,312.00	£3.31	BNF: Gazyvaro 1000mg/40ml concentrate for solution for infusion vials (Roche Products Ltd)
Chlorambucil, Tablet, mg	2 mg	25	£42.87	£0.86	BNF: Chlorambucil 2mg tablets (Alliance Healthcare (Distribution) Ltd)
Ibrutinib, Tablet	140 mg	90	£4,599.00	£0.37	BNF: Imbruvica 140mg capsules (Janssen-Cilag Ltd)
	140 mg	120	£6,132.00	£0.37	

Abbreviations: BNF: British National Formulary; IV: intravenous.

Table 50: Treatment regimens for VenG and comparators

Regimen	Drug	Admin	Dosing schedule	Cost per cycle	Trial name (Reference)
VenG	Venetoclax	Oral	Venetoclax: • 20 mg daily during Cycle 1, Days 22−28 • 50 mg daily during Cycle 2, Days 1−7 • 100 mg daily during Cycle 2, Days 8−14 • 200 mg daily during Cycle 2, Days 15−21 • 400 mg daily during Cycle 2, Days 22−28 and on Days 1−28 for all subsequent cycles until the end of Cycle 12	Cycle 1, Days 22−28: £59.87 Cycle 2, Days 1−7: £149.67 Cycle 2, Days 8−14: £299.34 Cycle 2, Days 15-21: £598.68 Cycle 2, Days 22−28: £1,197.37 Cycle 3–12:	CLL14[1]

				£4,789.47	
	Obinutuzumab	IV	• 100 mg on Day 1 and 900 mg on Day 2 (or 1000 mg on Day 1) • 1000 mg at Cycle 1, Day 8 and Day 15 • 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6	£9,936 for Cycle 1 £3,312 for Cycle 2–6	CLL14[1]
GClb	Obinutuzumab	IV	• 100 mg on Day 1 and 900 mg on Day 2 (or 1000 mg on Day 1) • 1000 mg at Cycle 1, Day 8 and Day 15 • 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6	£9,936 for Cycle 1 £3,312 for Cycle 2–6	CLL14[1]
	Chlorambucil	Oral	0.5 mg/kg at Day 1 and Day 15 for Cycles 1−12	Assuming a weight of 76: £64.79	CLL14[1]
Ibr	Ibrutinib	Oral	420 mg daily continuously (until evidence of progressive disease or no longer tolerated by the patient)	£4292	RESONATE [101]

Abbreviations: GClb: chlorambucil with obinutuzumab; Ibr: ibrutinib; IV: intravenous; VenG: venetoclax with obinutuzumab.

Administration costs

Obinutuzumab (comparator) and rituximab (subsequent treatment) are administered by intravenous infusion.

The treatment administration costs account for the staff costs in infusion procedures (Table 51). Millar et al. found that the dispensing of drugs administered intravenously takes on average 12 minutes each.[109] One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) is estimated to cost £46 (Hospital-based scientific and professional staff band 6 - Personal Social Services Research Unit (PSSRU) 2018, p52).[110] Hence 12 minutes of pharmacist time is associated with a cost of £9.20 per infusion (£46*12/60). In addition, the model considers alternative delivery methods, standard and rapid IV infusion methods, which imply different administration costs. The underlying assumption is that the cost of a rapid infusion would be similar to a simple chemotherapy delivery included in the NHS reference costs. The model's base case assumes that rituximab containing treatment (VenR) uses a 30:70 ratio between standard and Rapid IV infusions. This is based on a survey that was conducted within 20 UK trusts regarding their administration policies. The administration cost of standard IV infusion was applied to obinutuzumab.

Table 51 Drug administration costs

Drug	Cost	Currency code	Description
IV standard	£298.53 (= £289.33 + £9.20)	SB15Z	IV administration cost from NHS Reference Costs 2017-18; Total HRGs, SB15Z: deliver subsequent elements of a chemotherapy cycle. This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.20).
Rituximab (IV Rapid)	£238.19 (= £228.99 + £9.20)	SB12Z	IV administration cost from NHS Reference Costs 2017-18; Total HRGs, SB12Z: deliver Simple Parenteral Chemotherapy at First Attendance. This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.20).

Abbreviations: IV: intravenous; HRG: Healthcare Resource Group; NHS: National Health Service

Routine care and monitoring costs

Table 52 presents the resource use categories included in the model, which were informed by discussion with five clinicians at an AbbVie-organised advisory board.

Table 52: Pre- and post-progression annual resource use frequency

Resource use	Annual pre-progression frequency	Annual post-progression frequency	Per cycle pre-progression frequency	Per cycle post-progression frequency
Full blood count*	4	4	0.31	0.31
LDH	2	2	0.15	0.15
Haematologist visit	4	4	0.31	0.31
CT Scan	2	2	0.15	0.15
Biochemistry test: renal - Urea and electrolytes test	3	2	0.23	0.15
Biochemistry test: liver function test	3	2	0.23	0.15
Immunoglobulins Blood Test	3	2	0.23	0.15
Inpatient non-surgical/medical visit	0	3	0	0.23
Full blood transfusion	0	1	0	0.08

*Lymphocyte count (if not already included in full blood count)
Abbreviations: CT: computerised tomography; LDH: lactate dehydrogenase.

The most recent national reference costs schedule (i.e. 2017/18)[111] were used to inform the routine care and monitoring costs shown in Table 53.

Table 53: Routine care and monitoring costs used in the model

Routine care and monitoring costs	Value	HRG codes from reference costs 2017/18[111]
Full blood count	£2.51	DAPS05- Haematology
LDH	£1.11	DAPS04 - Clinical biochemistry

Haematologist visit	£159.65	Outpatient Attendances Data: 303- Clinical haematology
Inpatient non-surgical/medical visit	£572.78	National schedule of reference costs 2017/18: Weighted average of day case, Chronic Lymphocytic Leukaemia, including Related Disorders, SA32A (£396), SA32B (£428), SA32C (£379) and SA32D (£449) = £432.93 PSSRU 2018: Medical consultant hour (£108) + qualification costs (£31.846) = £139.846
Full blood transfusion	£187.97	Outpatient Procedures- 303, Clinical Haematology, single plasma exchange or other intravenous blood transfusion, 19 years and over (SA44A)
CT Scan	£92.81	Weighted average of RD20A (£88) and RD21A (£106)[29]
Biochemistry test: renal - Urea and electrolytes test	£1.11	DAPS04 – Clinical biochemistry
Biochemistry test: liver function test	£1.11	DAPS04 - Clinical biochemistry
Immunoglobulins Blood Test	£2.51	DAPS05- Haematology (assumed to be equal to full blood count)

Abbreviations: CT: computerised tomography; HRG, Healthcare Resource Group; LDH, Lactate Dehydrogenase; PSSRU, Personal Social Services Research Unit.

Treatment-specific monitoring costs – Tumour lysis syndrome

The costs for laboratory TLS prophylaxis are obtained based on an algorithm (detailed in Appendix M) considering the TLS risk distribution of patients from the treated CLL14 population. The TLS prophylaxis is applied to both VenG and GClb treatment arms, since the CLL14 trial protocol states that patients administered venetoclax and obinutuzumab should be monitored for TLS.

Specifically, patients were first divided into patients at lower and greater risk based on the tumour mass and absolute lymphocyte count (ALC) (i.e. lower risk: lymph node with a diameter ≤5 cm and ALC <25 x 10^9/L; greater risk included all other patients).

Patients in the lower risk group included 13.43% of VenG patients and 12.04% GClb patients. Patients in the greater risk included 86.57% in the VenG arm and 87.96% in the GClb arm. The greater risk group was subdivided into two groups according to Creatinine Clearance. The TLS risk group distribution split by treatment arm is provided in Table 54.

Table 54: TLS risk distribution for VenG and GClb treatment arm

Treatment	Lower Risk (node diameter ≤5 cm and ALC <25 x 10^9)	Greater Risk (node diameter >5 cm or ALC >25 x 10^9)	
		Creatinine clearance > 80 mL/min	Creatinine clearance ≤ 80 mL/min
VenG	[redacted]	[redacted]	[redacted]
GClb	[redacted]	[redacted]	[redacted]

Abbreviations: ALC: absolute lymphocyte count; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

Table 55 provides the cost split by risk of tumour burden and also by treatment arm. Please note the costs for the greater risk tumour burden patients are different across the VenG and GClb

arms because the proportion of patients who receive rasburicase (an antihyperuricaemic agent used to prevent TLS) at baseline is different across these treatment arms.

Table 55: TLS cost split by tumour burden in each treatment arm

Treatment	Low tumour burden	Greater Risk (CrCl >80)	Greater Risk (CrCl ≤80)	Total cost used in model
VenG	£1447.59	£1745.36	£2247.74	£1933
GClb	£1447.59	£1525.64	£2259.85	£1694

Abbreviations: CrCl: creatinine clearance; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

Based on the TLS risk distribution and the prophylaxis algorithm, the cost of TLS prophylaxis applied to the VenG arm in the first cycle is £1,933 and in the GClb arm in the first cycle is £1,694. The cost is lower in the GClb arm because there are fewer high-risk patients in the GClb arm compared to the VenG arm.

Subsequent treatment costs

When applying subsequent treatment costs three key inputs are required:

- **The type of treatment mix received** – UK-based clinical experts were consulted and the treatment mix per treatment arm and population were included to inform the subsequent treatment line treatment mix (Table 56). Extreme value scenario testing is also explored in scenario testing to assess the impact these have on ICER values.
- **The timepoint at which the patients who are eligible to receive the next treatment line will be receiving therapy** – the time to next treatment curves for VenG and GClb were adjusted for overall survival from the CLL14 trial to identify the time points at which patients would move to the next line of treatment.
- **How long subsequent (second line) treatment is received**, i.e. how long patients stay on second line and when they move to the third line of treatment – values from literature were used to inform this input. Table 57 provides the median time of treatment identified in the most recent literature sources which were chosen given the rapidly changing treatment landscape of CLL patients. These treatment durations have also been validated by UK-based clinical experts. For the del(17p)/*TP53* mutation population, the difference in the PPS duration and OS curve from the ibrutinib treatment was used to inform the proportions of patients who receive subsequent treatment and are still alive.

Table 56: Overview of base case subsequent treatment mix

Initial treatment	Subsequent treatment	
	Non-del(17p)/*TP53* mutation	del(17p)/*TP53* mutation
VenG	50% ibrutinib; 50% VenR	100% ibrutinib
GClb	50% ibrutinib; 50% VenR	N/A
Ibrutinib	N/A	100% venetoclax monotherapy

Abbreviations: GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Table 57: Subsequent treatment durations used in the model

Subsequent treatment	Median duration, months	Source
VenR	24.4	Kater et al. (2019);[112]
Ibrutinib	39.00	O'Brien et al. (2018)[113]
Venetoclax monotherapy	16.00	Davids et al. (2018)[114]

Abbreviations: VenR: venetoclax with rituximab.

Table 58 provides an overview of all the drug costs for subsequent treatments included in the budget impact analysis along with the cost per pack size and the cost per mg of the drug. The treatment regimens for subsequent treatments are summarised in Table 59.

Table 58: Drug costs for subsequent treatments

Drug	Dose per tablet or vial	Units per package	Cost per package	Price per mg	Source
Venetoclax Tablet, mg	10 mg	14	£59.87	£0.43	BNF: Venclyxto (AbbVie Ltd)
	50 mg	7	£149.67	£0.43	
	100 mg	7	£299.34	£0.43	
	100 mg	14	£598.68	£0.43	
	100 mg	112	£4,789.47	£0.43	
Rituximab, IV	500 mg	1	£785.84	£1.57	BNF: Truxima 500mg/50ml concentrate for solution for infusion vials (Napp Pharmaceuticals Ltd) IV administration cost from NHS Reference Costs 2017-18; Total HRGs, SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance (£240.07). This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.00).
Ibrutinib, Tablet	140 mg	90	£4,599.00	£0.37	BNF: Imbruvica 140mg capsules (Janssen-Cilag Ltd)
	140 mg	120	£6,132.00	£0.37	

Abbreviations: BNF: British National Formulary; IV: intravenous; PSSRU: Personal Social Services Research Unit; VenG: venetoclax with obinutuzumab.

Table 59: Treatment regimens for subsequent treatments

Regimen	Drug	Admin	Dosing schedule	Cost per cycle	Trial name (Reference)

VenR	Venetoclax	Oral	Venetoclax: • In the titration phase, 20 mg orally once daily for 7 days, increasing by gradual weekly increments over 5 weeks to 400 mg once daily • In the post-titration phase, 400 mg orally once daily Venetoclax can be taken for a maximum of 2 years from day 1 of cycle 1 of rituximab, or until disease progression or unacceptable toxicity	Cycle 1, Days 22−28: £59.87 Cycle 2, Days 1−7: £149.67 Cycle 2, Days 8−14: £299.34 Cycle 2, Days 15-21: £598.68 Cycle 2, Days 22−28: £1,197.37 Cycle 3 onwards: £4,789.47	MURANO[115]
	Rituximab	IV (By body surface area [BSA])	Rituximab should be administered after the patient has completed the dose-titration schedule and has had the recommended daily dose of 400 mg venetoclax for 7 days. • Rituximab 375 mg/m^2 is given intravenously on day 1 of cycle 1 (a cycle is 28 days), followed by 500 mg/m^2 on day 1 of cycles 2 to 6. Rituximab is stopped after cycle 6.	Assuming vial sharing and a BSA of 1.88 m^2: Cycle 1: £1106.85 Cycle 2–6: £1475.80 Assuming no vial sharing and a BSA of 1.88 m^2: Cycle 1–6: £1571.68	MURANO[115]
Ibr	Ibrutinib	Oral	420 mg daily continuously (until evidence of progressive disease or no longer tolerated by the patient)	£4292	RESONATE[101]
Ven mono	Venetoclax	Oral	• In the titration phase, 20 mg orally once daily for 7 days, increasing by gradual weekly increments over 5 weeks to 400	Cycle 1, Days 22−28: £59.87 Cycle 2, Days 1−7:	SmPC

			mg once daily • In the post-titration phase, 400 mg orally once daily Treatment should be continued until disease progression or no longer tolerated by the patient	£149.67 Cycle 2, Days 8−14: £299.34 Cycle 2, Days 22−28: £598.68 Cycle 3 onwards: £4,789.47	

Abbreviations: BSA: body surface area; Ibr: ibrutinib; IV: intravenous; O: ofatumumab; R: rituximab; SmPC: Summary of Product Characteristics; VenR: venetoclax with rituximab.

Table 60: Overview of base case subsequent treatment mix

Initial treatment	Subsequent treatment	
	Non-del(17p)/*TP53* mutation	del(17p)/*TP53* mutation
VenG	50% ibrutinib; 50% VenR	100% ibrutinib
GClb	50% ibrutinib; 50% VenR	N/A
Ibrutinib	N/A	100% venetoclax monotherapy

Abbreviations: GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

B.3.5.2 Health-state unit costs and resource use

There are no costs related to specific health-states.

B.3.5.3 Adverse reaction unit costs and resource use

Adverse event costs were aligned with those accepted in TA561, with small changes made to the costs for neutropenia, leukopenia, diarrhoea, and sepsis based on clinical feedback at an AbbVie-organised advisory board.[3] The costs were based on NHS Reference Costs, where available and past NICE appraisals, online national sources and literature as appropriate.

An overview of the adverse events costs and sources are provided in Table 61.

Table 61: Adverse event cost overview

Adverse event	Cost	PSA distribution	Source
Asthenia	£657.76	Gamma	TA498: National Schedule of Reference Costs 2017-18, non-elective short stay = £615.76 + PSSRU 2018, Cost of F2F community nurse contact = £42[116]
Diarrhoea	£0.34	Gamma	TA344;[68] Woods et al. (2012)[117]); Loperamide price BNF: cost per mg = £0.97 / 60 mg = £0.016; total costs = £0.016 * 21 mg = £0.3395
Dyspnoea	£591.49	Gamma	NHS Reference Costs 2017-18; Total - HRGs, Other Respiratory disorders without interventions

			(weighted average of DZ19L-DZ19N [£1,132], DZ19M [£725] and DZ19N [£475])[110]
Febrile neutropenia	£6,563.61	Gamma	NICE TA359: NHS Reference Costs 2012-13; Total- HRGS, PA45Z. Inflated by four years using the PSSRU HCHS index (£5993.03*1.026*1.019*1.022*1.025).[110]
Infusion related reaction	£432.93	Gamma	NHS reference costs 2016-2017: Weighted average of day case, Chronic Lymphocytic Leukaemia, including Related Disorders, SA32A (£396), SA32B (£428), SA32C (£379) and SA32D (£449).
Leukopenia	£535.56	Gamma	Same as neutropenia
Neutropenia	£535.56	Gamma	Cost of lenograstim for 8 days (median duration of neutropenia in MURANO trial - Seymour et al. 2018)
Pneumonia	£6167.48	Gamma	NHS Reference Costs 2017-18; Total - HRGs, Lobar, Atypical or Viral Pneumonia, with multiple interventions (weighted average of DZ11K (£7,803), DZ11L (£6,226) and DZ11M (£4,364)[110]
Sepsis	£6167.48	Gamma	Same as pneumonia
Thrombocytopenia	£640.09	Gamma	NHS Reference Costs 2017-18; Total - HRGs, Thrombocytopenia (weighted average of SA12G (£1,892), SA12H (£930), SA12I (£549) and SA12K (£372)[110]

Abbreviations: BNF: British National Formulary; HCHS: hospital and community health services; HRG: Healthcare Resource Group; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

B.3.5.4 Miscellaneous unit costs and resource use

Terminal care costs

Costs associated with terminal care are included in the model. These are applied to all patients who transition to the death health state as a one-off cost. The NICE appraisal TA561 sourced the terminal care costs from a published study on end-of-life care for solid tumour cancer patients.[118] The specific cost used was guided by the NICE ibrutinib appraisal, TA429.[34] Clinical experts advising on the ibrutinib submission process had suggested that the costs of terminal care would be similar between solid tumour and haematology patients.

The terminal care costing study incorporated Bayesian modelling using data from the literature and publicly available datasets. Four types of cancer were considered: Breast, Colorectal, Lung and Prostate. Mean costs were presented for health care, social care, charity care and informal care. The cost used within the economic model only considers the direct costs borne by the health and social care sectors, in line with the perspective recommended in the NICE reference case. The costs are presented below in Table 62. The total cost for terminal care per patient was £6,662.15 (inflated to 2017–18 prices).[110]

Table 62: Terminal care costs

Resource category	Mean costs (2013-14)	HCHS annual price inflation multiplier (to 2017-18)	Mean total cost (2018)
Health care	£4,254	1.026*1.019*1.022*1.025 = 1.095	£6,662.15
Social care	£1,829		
Total	£6,083		

Abbreviations: HCHS: Hospital and Community Health Services

B.3.6 *Summary of base case analysis inputs and assumptions*

B.3.6.1 Summary of base case analysis inputs

Table 63: Summary of base case analysis inputs

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model properties			
Perspective	NHS/PSS	None	B.3.2.2
Time horizon	Lifetime (30-years)	None	B.3.2.2
Cycle length	28 days	None	B.3.2.2
Population	• Patients with previously untreated CLL without del(17p)/*TP53* mutation • Patients with previously untreated CLL with del(17p)/*TP53* mutation	None	B.3.2.1
Age (mean age of cohort)	Non-del(17p)/*TP53*: 71.1 Del(17p)/*TP53*: 69.6	Normal	B.3.3.1
% male patients	Non-del(17p)/*TP53*: 66.4% Del(17p)/*TP53*: 67.7%	Beta	B.3.3.1
BSA (m^2)	Non-del(17p)/*TP53*: 1.9 Del(17p)/*TP53*: 1.9	Normal	B.3.3.1
Weight (kg)	Non-del(17p)/*TP53*: 75.6 Del(17p)/*TP53*: 78.2	Normal	B.3.3.1
Discount rates for costs and benefits	3.5%	None	B.3.2.2
Primary endpoint	PFS	None	B.3.3.4
Source of AE incidence	VenG and GClb: CLL14[1] Ibrutinib: Barr 2018[101]	Gamma	B.3.3.11
Non-del(17p)/*TP53*			
Source of effectiveness – PFS	VenG: Independent model, log-logistic	None	B.3.3.4

	GClb: Independent model, log-logistic		
Source of effectiveness – OS	Dependent model, exponential distribution No treatment effect assumed	None	B.3.3.5
Source of effectiveness – TTNT	VenG: Independent model, Weibull GClb: Independent model, Weibull	None	B.3.3.6
ToT	Non-del(17p) ToT curves per treatment arm from CLL14 trial	None	B.3.3.7
del(17p)/*TP53*			
Source of effectiveness – PFS	VenG: Independent model, log-logistic Ibrutinib: Mato HR	Log-normal	B.3.3.10
Source of effectiveness – OS	VenG: Dependent model, exponential distribution Ibrutinib: Mato HR	Log-normal	B.3.3.10
Source of effectiveness – TTNT	VenG: Independent model, Weibull Ibrutinib: Incident patients who have progressed and not died	Normal	B.3.3.10
ToT	VenG: Del(17p) ToT curve for VenG from CLL14 trial Ibrutinib: PFS curve for ibrutinib	None	B.3.3.10
Utilities			
Health state utilities	TA343[67]	Beta	B.3.4.5
AE utility decrements	Previous NICE appraisals	Gamma	B.3.4.4
Costs			
Active treatment costs	BNF	None	B.3.5.1
Routine care and monitoring costs	National reference costs 2017/18[111]	Gamma	B.3.5.1
Subsequent treatment costs	BNF	Beta or Dirichlet	B.3.5.1
Adverse events monitoring costs	NICE appraisal TA561[3]	Gamma	B.3.5.3
Terminal care costs	NICE appraisal TA429[34]	Gamma	B.3.5.4

Abbreviations: AE: adverse event; BNF: British National Formulary; BSA: body surface area; CLL: chronic lymphocytic leukaemia; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; NHS: National Health Service; OS: overall survival; PFS: progression-free survival; PSS: Personal and Social Services; ToT: time-on-treatment; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

B.3.6.2 Assumptions

Table 64 provides an overview of a number of assumptions which should be taken into consideration when assessing the results provided in Section B.3.6.

Table 64: Model assumptions

Model input	Assumption

Survival model	
OS curves	• Due to immature OS data and given that the VenG PFS leads to a clinically important and statistically significant gain in PFS compared to GClb, and in the absence of recent and relevant data, the model assumes no treatment effect. This assumption was validated with experts. Therefore, the total life years of VenG and GClb are equal • The proportional hazards assumption cannot be rejected leading to the dependent model being used. An exponential distribution is used, based on clinical expert opinion
PFS curve	• The proportional hazards assumption does not hold leading to use of independent models for each treatment arm being used (VenG and GClb) • A log-logistic distribution was chosen, based on clinical expert opinion and validation of the GClb treatment arm (using CLL14 trial data that were also validated with CLL11 published landmark data for the GClb arm)
TTNT	• The proportional hazards assumption does not hold leading to use of independent models for each treatment arm being used (VenG and GClb) • A Weibull distribution was chosen, based on statistical fit and validation of the GClb treatment arm (using CLL14 trial data that were validated with published CLL11 data for GClb arm) • Ibrutinib arm assumes difference in PPS duration and OS curve to inform the patients on subsequent treatment line
Indirect Treatment Comparison	
del(17p)/*TP53*	• Neither an NMA nor MAIC were feasible to be conducted • Therefore, the comparison with ibrutinib is a naïve comparison of single arm studies and is a non-significant estimate using a recently published source: Mato et al. 2018[60]
Costs	
Adverse event costs	• Neutropenia costs are assumed to be the same as for treatment with lenograstim (glycosylated rhG-CSF) • Leukopenia cost is assumed to be the same as for neutropenia • Diarrhoea cost is assumed to be the same as for treatment with loperamide • Sepsis cost is assumed to be the same as for pneumonia
Adverse event rates	• Adverse events are assumed to occur within the first cycle of the model
Routine care and monitoring costs	• Immunoglobulins blood test cost is assumed to be the same as full blood count cost
TLS Prophylaxis cost	• Greater risk patients are assumed to be hospitalised for one day during weeks 1 and 2 of prophylaxis
Treatment costs	• Ibrutinib uses its own PFS curve to inform the total number of patients receiving treatment per cycle

	• VenG and GClb use the ToT curve from the trial to inform the total number of patients receiving treatment per cycle up until the end of the fixed treatment duration period
Wastage cost	• Wastage costs are assumed for the base case as a conservative assumption
Utilities	
Adverse event HRQoL	• Adverse events are associated with one-off costs and negative HRQoL impacts • Leukopenia and neutropenia disutility values are assumed to be the same • Pneumonia disutility is assumed to be the same as for infection related disutility • Disutility from incidence of adverse event is not captured in the utility level for the health state
Utilities	• The same utilities are assumed for del(17p)/*TP53* mutation and non-del(17p)/*TP53* mutation populations across all treatment arms. For pre-progression health state, TA343 utilised values were for intravenous treatment and are applied until progression. This is a conservative assumption since VenG and GClb are with a fixed treatment duration of 12 months but was adopted to simplify an overall complex economic evaluation.
Subsequent treatment costs	
Treatment mix	• The subsequent treatment mix received is assumed based on clinical expert opinion. Conservative assumptions were applied as base case for the VenG arm.

Abbreviations: GClb: chlorambucil with obinutuzumab; G-CSF: granulocyte-colony stimulating factor; HRQoL: health-related quality-of-life; MAIC: matching adjusted indirect treatment comparison; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; TLS: tumour lysis syndrome; ToT: time-on-treatment; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

B.3.7 *Base case results*

Base case results for the cost-effectiveness analysis are presented in the following subsections, for both the del(17p)/*TP53* and non-del(17p)/*TP53* populations. Base case results are presented as follows:

- List price VenG vs list price of all comparators (GClb and ibrutinib)
- PAS price of venetoclax only (obinutuzumab remains at list price) vs list price of all comparators (GClb and ibrutinib)

The Evidence Review Group (ERG) will undertake similar comparisons using the confidential discounted prices for obinutuzumab and ibrutinib and share these with the appraisal committee.

B.3.7.1 Base case incremental cost-effectiveness analysis results

The base case deterministic cost-effectiveness results are provided for list price and with venetoclax PAS price in Table 65 and Table 66, respectively. VenG was associated with higher average QALYs and lower average costs vs GClb in the non-del(17p)/*TP53* mutation population, and vs ibrutinib in the del(17p)/*TP53* mutation population, meaning that VenG is dominant vs both comparators.

In the non-del(17p)/*TP53* mutation population, cost-effectiveness is largely driven by an increase in progression-free life years, and a reduction in subsequent costs following progression compared to GClb. In the del(17p)/*TP53* mutation population, the driver of the ICER values is the medication costs of ibrutinib (treatment conditions until patients progress; mean of 45 months) vs fixed treatment duration for VenG (mean of 9.8 months; see section B.3.3.1 and B.3.3.8).

Table 65: Base case results at VenG list price (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	14.520	6.472				
VenG	[redacted]	14.520	6.837	[redacted]	0.000	0.365	VenG is Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	5.340	2.955				
VenG	[redacted]	5.460	2.991	[redacted]	0.119	0.036	VenG is Dominant

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Table 66: Base case results at venetoclax PAS price* (deterministic)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	14.520	6.472				
VenG	[redacted]	14.520	6.837	–£183,555	0.000	0.365	VenG is Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	5.340	2.955				
VenG	[redacted]	5.460	2.991	–£191,701	0.119	0.036	VenG is Dominant

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 simulations, in order to calculate the uncertainty in costs and outcomes. In cases where uncertainty data was not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The base case probabilistic results for list price and with venetoclax PAS price are provided in Table 67 and Table 68, respectively. The probabilistic results are broadly in line with the deterministic results, showing that the model is relatively stable when tested for uncertainty and that VenG is dominant vs both GClb and ibrutinib.

Table 67: Base case results at VenG list price (probabilistic)

Treatment	Total costs, £ (95% CI)	Total LYG	Total QALYs (95% CI)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	NR	6.434 (5.431, 7.361)				
VenG	[redacted]	NR	6.785 (5.534, 7.927)	[redacted]	NR	0.351	VenG is Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	NR	3.005 (1.486, 4.816)				
VenG	[redacted]	NR	3.020 (1.571, 4.880)	[redacted]	NR	0.015	VenG is Dominant

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Table 68: Base case results at venetoclax PAS price* (probabilistic)

Treatment	Total costs, £ (95% CI)	Total LYG	Total QALYs (95% CI)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	NR	6.416 (5.459, 7.349)				
VenG	[redacted]	NR	6.764 (5.614, 7.932)	–£164,658	NR	0.348	VenG is Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	NR	2.997 (1.567, 4.756)				
VenG	[redacted]	NR	3.020 (1.574, 4.762)	–£143,423	NR	0.007	VenG is Dominant

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab. **Abbreviations**: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Non-del(17p)/*TP53* mutation population (VenG versus GClb)

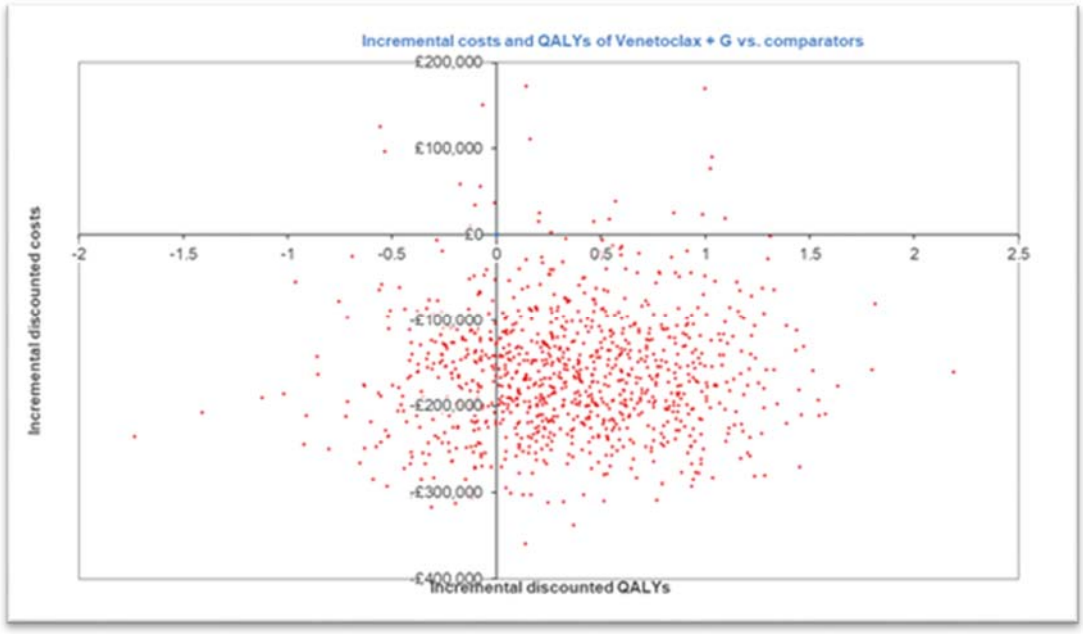
The model results from the PSA are presented in the scatter plot at list price in Figure 37 and at venetoclax PAS price in Figure 38. Uncertainty can be seen surrounding QALYs, since the uncertainty in QALYs is driven by the uncertainty in the extrapolations seen in the survival curves. Similar to the deterministic results, VenG is [redacted] over GClb in the PSA also.

The total cost and QALY estimates are comparable between the deterministic and the probabilistic analyses (differ by [redacted] for incremental total costs at list price and [redacted] at venetoclax PAS price; and [redacted] for QALYs at list price and [redacted] at venetoclax PAS price due to stochastic variation between model runs).

Figure 39 and Figure 40 display the cost-effectiveness acceptability curve at different values of willingness-to-pay (WTP) at list price and venetoclax PAS price, respectively. At a £30,000 WTP threshold, VenG has over 90% probability of being cost-effective when compared to GClb.

Figure 37: Scatter plot of probabilistic results on the cost-effectiveness plane for non-del(17p)/*TP53* population – list price

Figure 38: Scatter plot of probabilistic results on the cost-effectiveness plane for non-del(17p)/*TP53* population – venetoclax PAS price*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

Figure 39: Cost-effectiveness acceptability curves for non-del(17p)/*TP53* population – list price

Figure 40: Cost-effectiveness acceptability curves for non-del(17p)/*TP53* population – venetoclax PAS price*

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

Del(17p)/*TP53* mutation population (VenG versus ibrutinib)

The model results from the PSA are presented in the scatter plot at list price in Figure 41 and at venetoclax PAS price in Figure 42. Significant uncertainty can be seen surrounding QALYs, since the uncertainty in QALYs is driven by the uncertainty in the extrapolations seen in the survival curves and the uncertainty in the PFS and OS HRs for the naïve comparison for ibrutinib versus VenG. Similar to the deterministic results, VenG is dominant over ibrutinib in the PSA also.

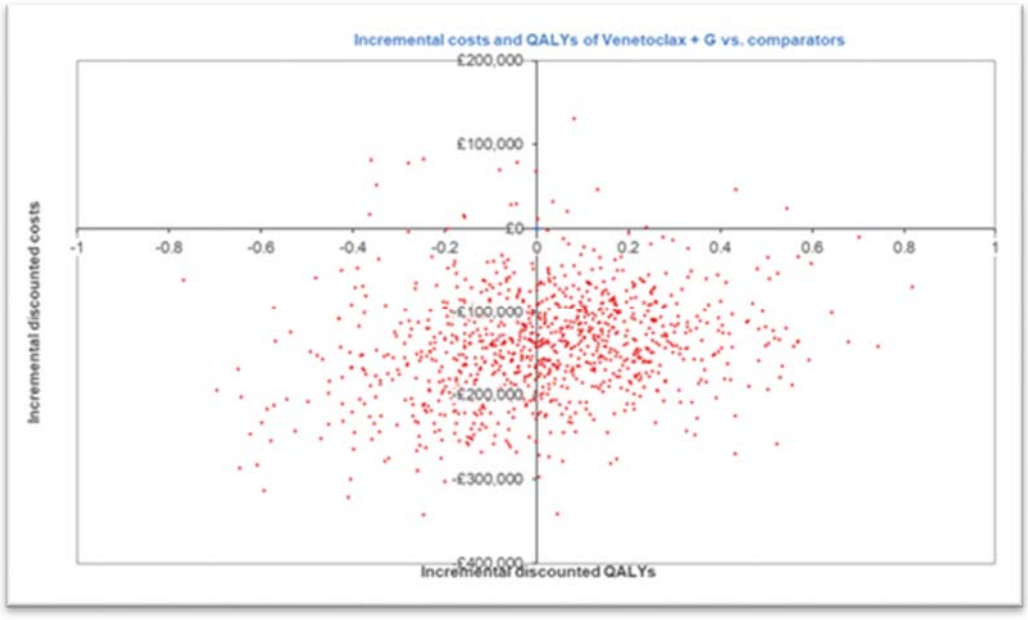
The total cost and QALY estimates are comparable between the deterministic and the probabilistic analyses (differ by [redacted] for incremental total costs at list price and [redacted] at venetoclax PAS price; and [redacted] for QALYs at list price and [redacted] at venetoclax PAS price, however these relative variations [redacted]).

Figure 43 and Figure 44 display the cost-effectiveness acceptability curve at different values of willingness-to-pay (WTP) at list price and venetoclax PAS price, respectively. VenG is observed to have a probability of being the cost-effective option of over 95% at a £30,000 WTP.

Figure 41: Scatter plot of probabilistic results on the cost-effectiveness plane for del(17p)/*TP53* population – list price

[redacted]

Figure 42: Scatter plot of probabilistic results on the cost-effectiveness plane for del(17p)/*TP53* population – venetoclax PAS price*

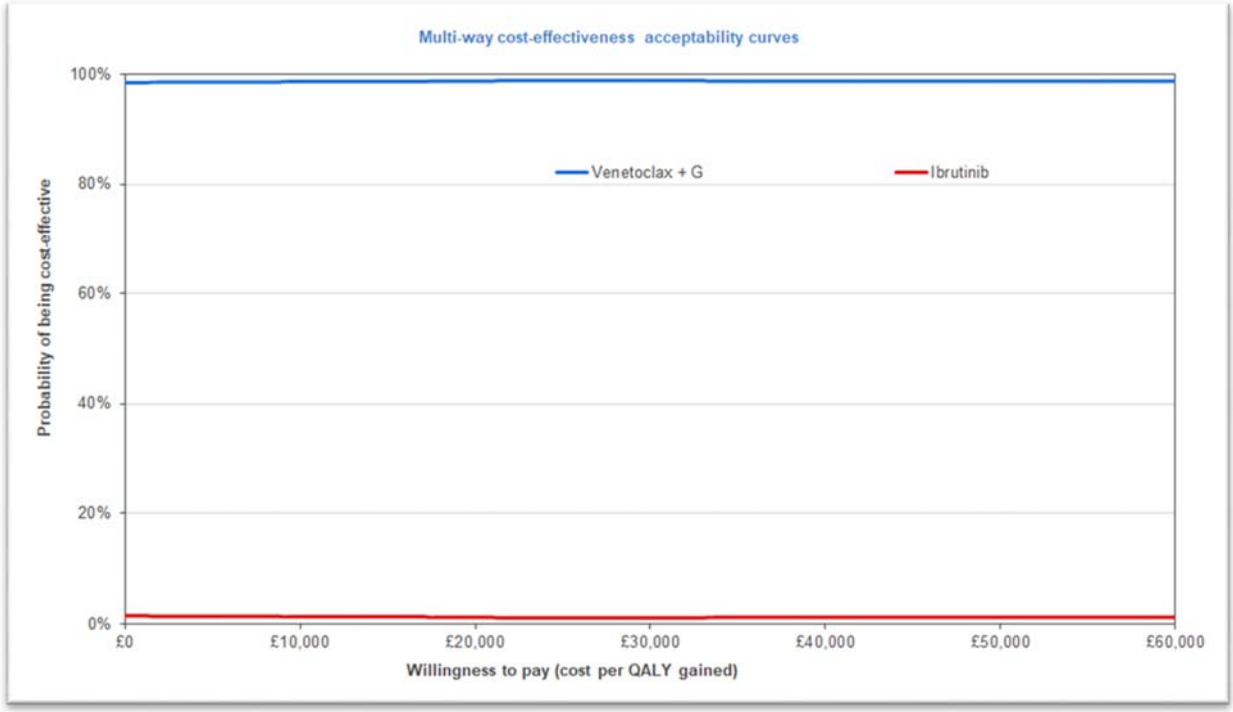


*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

Figure 43: Cost-effectiveness acceptability curves for del(17p)/*TP53* population – list price

[redacted]

Figure 44: Cost-effectiveness acceptability curves for del(17p)/*TP53* population – venetoclax PAS price*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

B.3.8.2 Deterministic sensitivity analysis

Non-del(17p)/*TP53* mutation population (VenG versus GClb)

Figure 45, Figure 46 and Figure 47 present the tornado plots from the one-way deterministic sensitivity analysis for incremental costs, QALYs and ICER, respectively, for VenG versus GClb at list price. Figure 48, Figure 49 and Figure 50 present the same data at venetoclax PAS price.

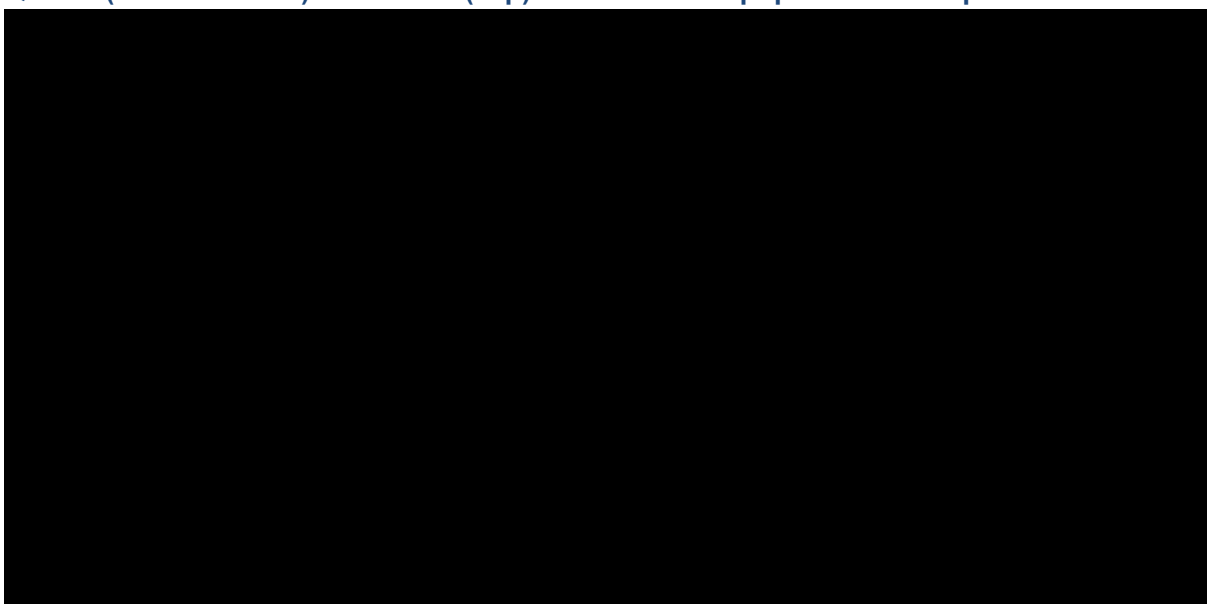
In cases where uncertainty data was not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The greatest impact on incremental costs is due to age. The age of patients drives the VenG and GClb survival curves and the survival curves are the key determinant of the incremental costs in the model. The greatest driver of incremental QALYs is the pre-progression survival utility value followed by the post-progression survival utility value. The overall driver of the incremental cost per QALY is the post-progression survival utility value. Since a large proportion of patients in the GClb arm remain in the post-progression survival period compared to VenG, the QALYs accrued in this health state have the largest impact on the incremental cost per QALY.

Figure 45: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG vs GClb) for non-del(17p)/*TP53* mutation population – list price

Abbreviations: GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Figure 46: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG vs GClb) for non-del(17p)/*TP53* mutation population – list price

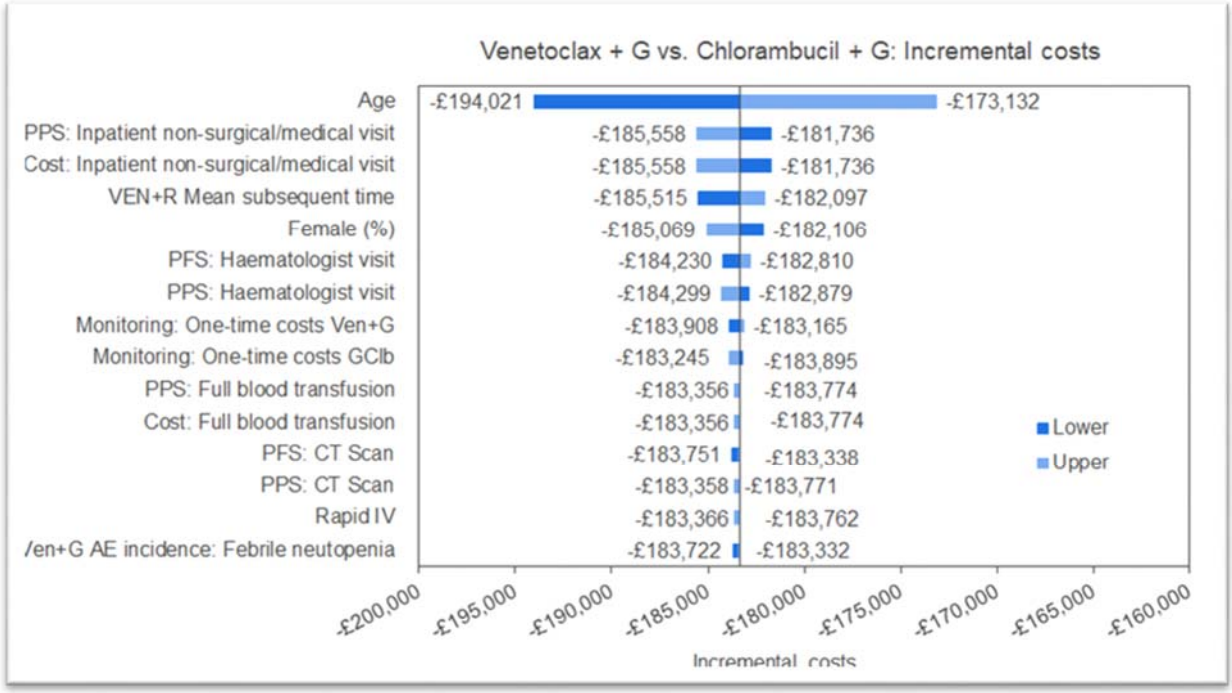


Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Figure 47: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG vs GClb) for non-del(17p)/*TP53* mutation population – list price

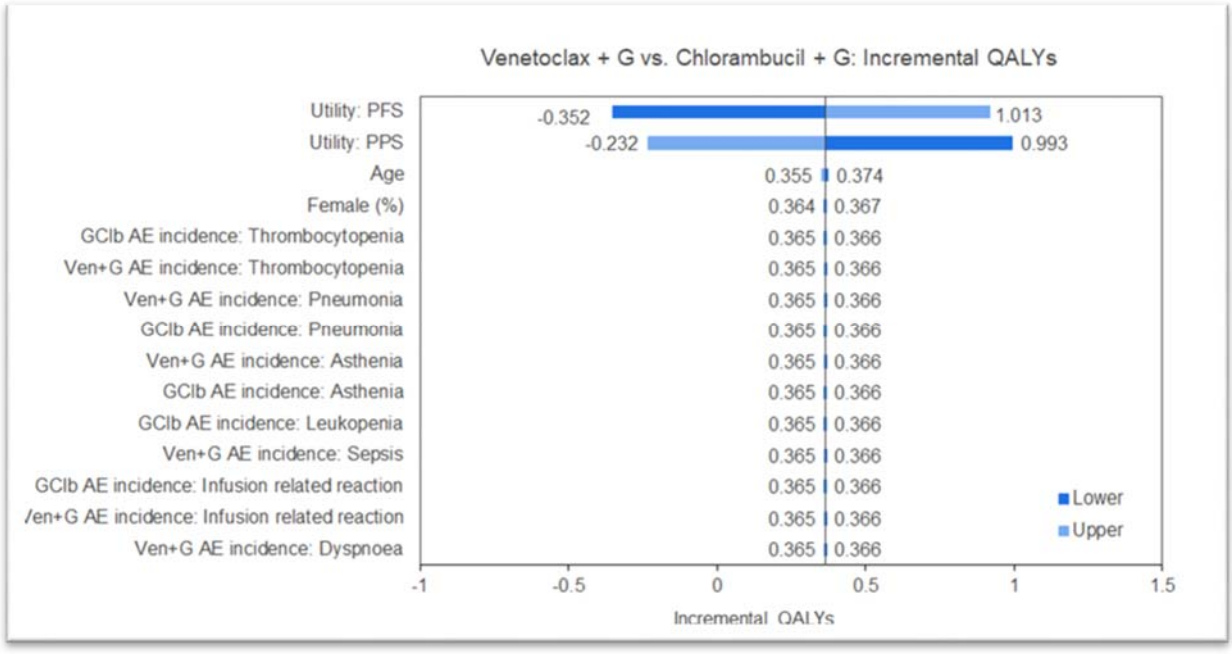
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Figure 48: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG vs GClb) for non-del(17p)/*TP53* mutation population – venetoclax PAS price*



Abbreviations: GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

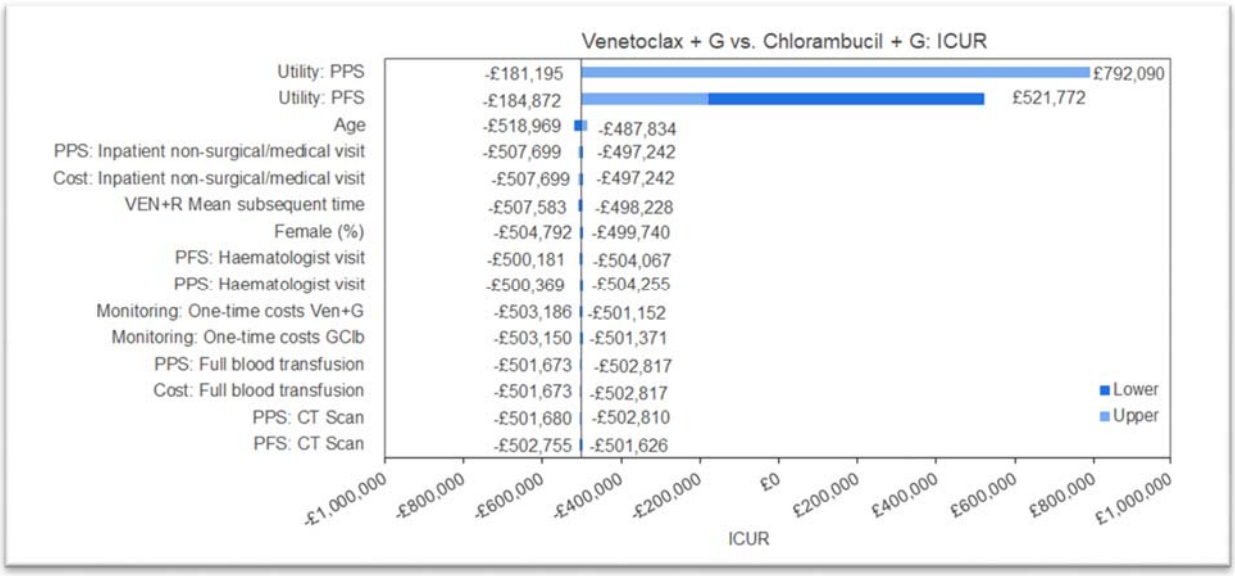
Figure 49: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG vs GClb) for non-del(17p)/*TP53* mutation population – venetoclax PAS price*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Figure 50: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG vs GClb) for non-del(17p)/*TP53* mutation population – venetoclax PAS price*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Del(17p)/*TP53* mutation population (VenG versus ibrutinib)

Figure 51, Figure 52 and Figure 53 present the tornado plots from the one-way deterministic sensitivity analysis for incremental costs, QALYs and ICER, respectively, for VenG versus ibrutinib. Figure 54, Figure 55 and Figure 56 present the same data at venetoclax PAS price.

The greatest impact on incremental costs and QALYs is due to the OS HR versus VenG. Whereas the PPS utility has the greatest impact on the ICER.

Figure 51: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG vs ibrutinib) for del(17p)/*TP53* mutation – list price

*IV category refers to intravenous costs.
Abbreviations: AE: adverse event; HR: hazard ratio; Ibr: ibrutinib; IV: intravenous; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

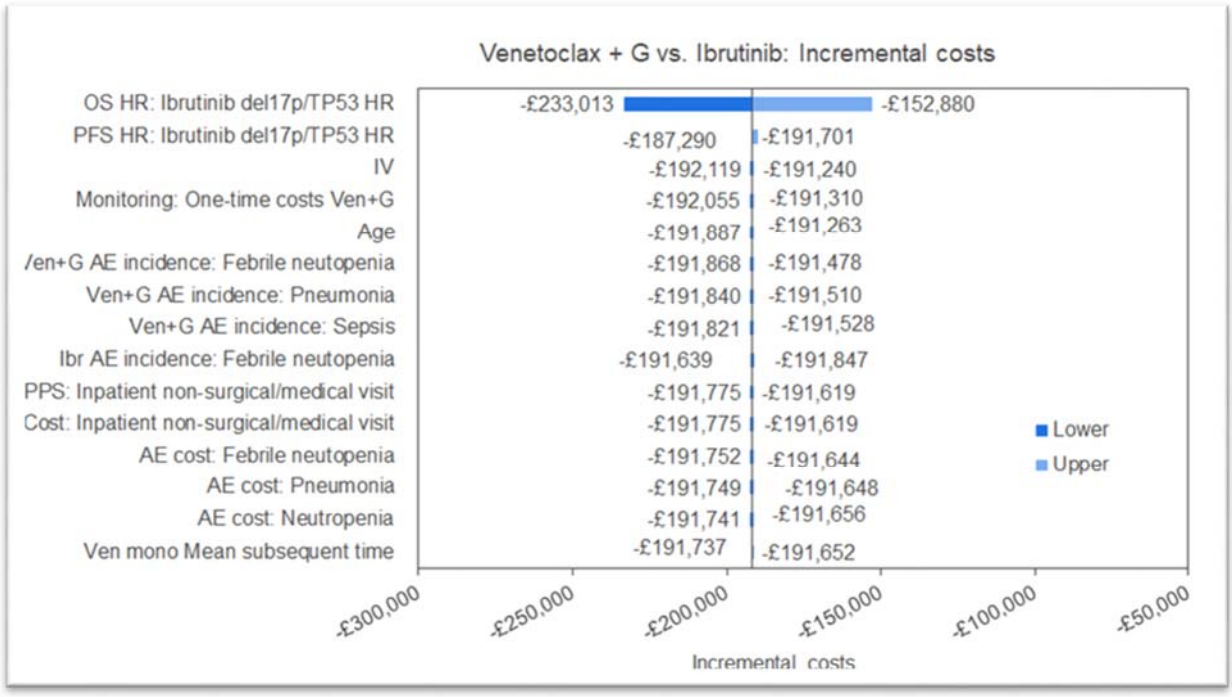
Figure 52: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG vs GClb) for del(17p)/*TP53* mutation – list price

Abbreviations: AE: adverse event; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life-year; VenG: venetoclax with obinutuzumab.

Figure 53: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG vs GClb) for del(17p)/*TP53* mutation – list price

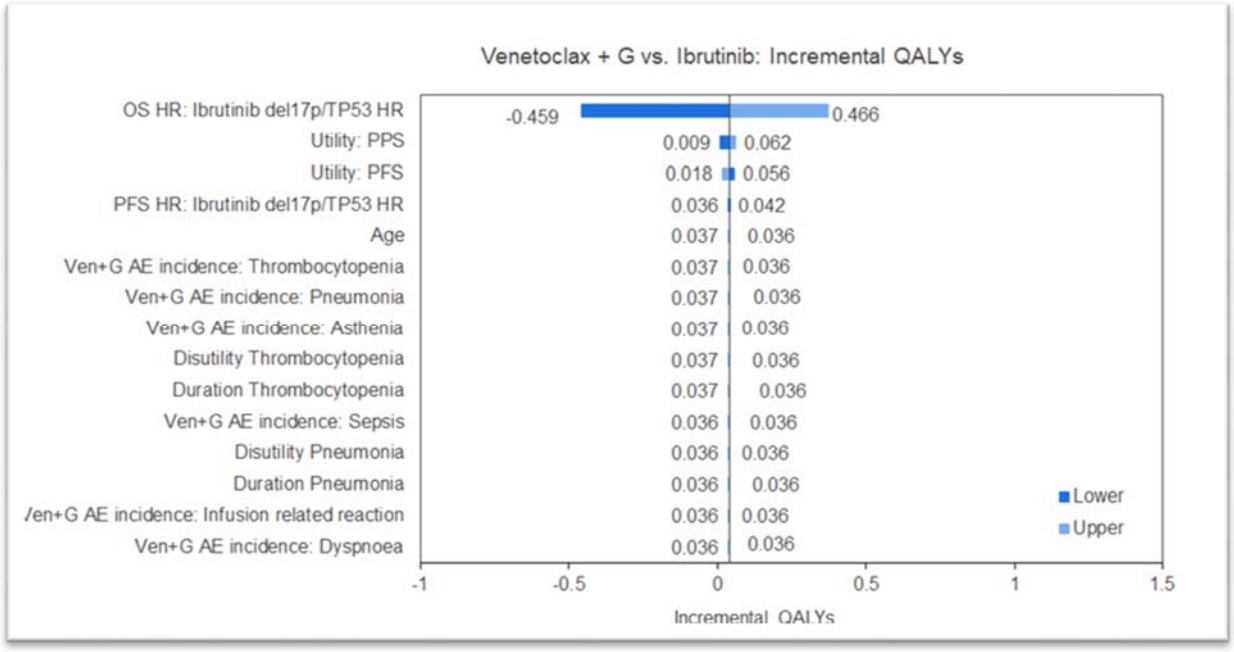
*IV category refers to intravenous costs
Abbreviations: AE: adverse event; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IV: intravenous; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

Figure 54: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG vs GClb) for del(17p)/*TP53* mutation population – venetoclax PAS price*



*IV category refers to intravenous costs.
Abbreviations: AE: adverse event; HR: hazard ratio; Ibr: ibrutinib; IV: intravenous; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

Figure 55: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG vs GClb) for del(17p)/*TP53* mutation population – venetoclax PAS price*



Abbreviations: AE: adverse event; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life-year; VenG: venetoclax with obinutuzumab.
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

Figure 56: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG vs GClb) for del(17p)/*TP53* mutation population – venetoclax PAS price*

*IV category refers to intravenous costs.
Abbreviations: AE: adverse event; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IV: intravenous; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.

B.3.8.3 Scenario analysis

All the scenarios and their respective descriptions are provided in Table 69. The scenario analysis results for the treatment comparators in the model are provided in Table 70 for the non-del(17)/*TP53* population and in Table 71 for the del(17p)/*TP53* population.

Table 69: Descriptions of the scenario analyses performed

<table>
<tr><th>Scenario</th><th>Description</th><th>Relevant population</th></tr>
<tr><td>Discount rates</td><td>The discount rates associated with costs and outcomes were varied between 0 and 6%</td><td rowspan="6">Applies to both populations</td></tr>
<tr><td>Time horizon</td><td>The time horizon was varied between 5, 10, 15, 20 and 25</td></tr>
<tr><td>Venetoclax TLS prophylaxis costs</td><td>The TLS costs of the venetoclax regimens were halved, doubled and removed</td></tr>
<tr><td>Adverse events</td><td>The adverse event rates were halved, doubled and removed.</td></tr>
<tr><td>Utilities</td><td>As literature-based values are used for the base case, EQ-5D-3L utility values from the CLL14 trial were assessed as a scenario. Pre-progression utility = 0.829. PPS utilities from the CLL14 trial were not tested due to very few patients having progressed. Furthermore, the PPS state extends from progression until death over many years and the few responses from the CLL14 trial were perforce very early in the PPS state.

Utilities used in the Venetoclax monotherapy NICE appraisal, TA487, were also tested as a scenario:[69]
Pre-progression: 0.748 (EQ-5D data study 116)
Post progression: 0.600 (Dretzke et al. 2010[61]) (This is the same post-progression utility used in the base case, so this remains unchanged)

Ibrutinib arm using utility value from TA343 for PFS under oral treatment (0.71) (Applied to del(17p)/*TP53* mutation population)
VenG and GClb arms, after 12 months of treatment, using utility value from TA343, PFS after initial treatment is completed (0.82) (Applied to non-del(17p)/*TP53* mutation population)</td></tr>
<tr><td>PPS CLL11</td><td>As suggested by clinicians at an AbbVie-organised advisory board but determined not to be the most plausible source. See Section B.3.3.6</td><td rowspan="3">Applies only to non-del(17p)/*TP53*</td></tr>
<tr><td>Resonate data
Warwick ERG NMA (Ibrutinib arm)</td><td>See Section B.3.3.6</td></tr>
<tr><td>Subsequent treatment scenarios</td><td><table><tr><th></th><th>VenG</th><th>GClb</th><th>Source/Assumption</th></tr><tr><td>Scenario 1</td><td>Ibrutinib: 100%</td><td>Ibrutinib: 100%</td><td>Assumption</td></tr></table></td></tr>
</table>

	Scenario 2	Ibrutinib: 100%	Ibrutinib 50% VenR 50%	Experts' opinion	
	Scenario 3	Ibrutinib: 100%	Ibrutinib 80% VenR 20%	Calculated from CLL14 subsequent treatment received by patients in each arm	
	Scenario 4	Ibrutinib 20% VenR 80%	Ibrutinib 80% VenR 20%	CLL14 median time off treatment is 17 months which could be considered as a late relapse (>12months) patients in VEN+G arm would be preferentially retreated with VenR (experts opinion)	
Wastage costs	Assuming no wastage cost				
Excess mortality risk	Adding additional mortality risk to background mortality hazards to generate 80% survival at 5 years. 10%, 15% and 19% excess risk of death to landmark.				
VenG survival model	These scenarios fit the survival models that were not selected as the base case (e.g. Weibull, lognormal, Gompertz, and generalised gamma). Since most of the uncertainty is to do with the OS RCT data, only the OS model was assessed for variable distributions. The dependent model was assessed since there is proportionality between the treatment arms. 1) All parametric distributions were run assuming no treatment effect exists for OS between the treatment arms. 2) All parametric distributions were run assuming treatment effect exists for OS between the treatment arms. This scenario also includes the base case distribution – exponential				Applies to both populations
PFS scenarios	Independent model and Dependent model using all distributions				
Extreme survival results scenarios	Using the PFS and OS curves that generate the lowest net monetary benefit, otherwise the distribution which generates the highest ICER				
Extreme value testing of comparison to ibrutinib PFS and OS hazard ratio (Source: Mato et al.)	Application of lower HR bounds (VenG least effective eventuality): a. HR= 0.293 for PFS b. HR= 0.334 for OS				Applies only to del(17p)/*TP53*

Abbreviations: EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version; ERG: Evidence Review Group; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; RCT: randomised controlled trial; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Non-del(17p)/*TP53* mutation population (VenG versus GClb)

Removing discount rates improves incremental QALYs for the comparators that accrue QALYs lower than VenG. Within the second scenario, which assesses shorter time horizons of 1–5

years, a large impact is observed on model results since VenG accrues fewer incremental QALYs over the shorter time period whilst the majority of VenG costs are captured within the first year. Changing TLS cost or adverse event rates do not have a large impact on the model. Changing utility values has a large impact on the incremental QALYs.

The effect of using alternative distributions for the OS dependent survival model (assuming either no treatment effect or treatment effect) does not lead to large changes in incremental results.

Applying the PPS CLL11 data has a significant impact (net monetary benefit [NMB]: 87% lower compared to base case) on the increment cost and QALYs versus GClb. However, VenG remains dominant over GClb due to OS being close to background mortality. Compared to the CLL11 scenario, the RESONATE (NMB: 32% lower compared to base case) and Warwick ERG NMA scenarios (NMB: 0.0035% lower compared to base case) have a less significant impact on cost and QALYs since the OS curves generated from these scenarios are closer to the CLL14 results than the ones generated using the CLL11 scenario.

Table 70: Scenario analysis for non-del(17p)/*TP53* mutation population

	List price				
	Incremental costs	**Incremental QALYs**	**Incremental LY**	**ICER**	**NMB**
Base case	[redacted]	**0.365**	**0.000**	**Dominant**	[redacted]
Discount rate. Costs: 0%, QALYs: 0%	[redacted]	0.513	0.000	Dominant	[redacted]
Discount rate. Costs: 0%, QALYs: 6%	[redacted]	0.295	0.000	Dominant	[redacted]
Discount rate. Costs: 6%, QALYs: 6%	[redacted]	0.295	0.000	Dominant	[redacted]
Discount rate. Costs: 6%, QALYs: 0%	[redacted]	0.513	0.000	Dominant	[redacted]
Time horizon: 5 year	[redacted]	0.076	0.000	[redacted]	[redacted]
Time horizon: 10 year	[redacted]	0.208	0.000	Dominant	[redacted]
Time horizon: 15 year	[redacted]	0.300	0.000	Dominant	[redacted]
Time horizon: 25 year	[redacted]	0.362	0.000	Dominant	[redacted]
TLS prophylaxis cost halved	[redacted]	0.365	0.000	Dominant	[redacted]
TLS prophylaxis cost doubled	[redacted]	0.365	0.000	Dominant	[redacted]
TLS prophylaxis cost removed	[redacted]	0.365	0.000	Dominant	[redacted]
Adverse event rates halved	[redacted]	0.366	0.000	Dominant	[redacted]
Adverse event rates doubled	[redacted]	0.365	0.000	Dominant	[redacted]
Adverse events removed	[redacted]	0.366	0.000	Dominant	[redacted]
Utility (from CLL14 trial)	[redacted]	1.196	0.000	Dominant	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
Pre-progression utility = 0.829					
Utility from Venetoclax monotherapy submission (pre-progression utility = 0.748; EQ-5D data study 116)	[redacted]	0.773	0.000	Dominant	[redacted]
VenG and GClb arms, after 12 months of treatment, using utility value from TA343 Progression-free survival after initial treatment is completed (0.82)	[redacted]	1.148	0.000	Dominant	[redacted]
CLL11	[redacted]	0.219	0.000	Dominant	[redacted]
RESONATE	[redacted]	0.337	0.000	Dominant	[redacted]
Warwick ERG – NMA	[redacted]	0.365	0.000	Dominant	[redacted]
Subsequent tx scenarios					
Scenario 1	[redacted]	0.365	0.000	Dominant	[redacted]
Scenario 2	[redacted]	0.365	0.000	Dominant	[redacted]
Scenario 3	[redacted]	0.365	0.000	Dominant	[redacted]
Scenario 4	[redacted]	0.365	0.000	Dominant	[redacted]
Wastage Cost Removed	[redacted]	0.365	0.000	Dominant	[redacted]
Excess risk of 90% added to background mortality to generate VEN+G survival of 80% at 5 years	[redacted]	0.303	0.000	Dominant	[redacted]
10% excess risk of death to Landmark	[redacted]	0.357	0.000	Dominant	[redacted]
15% excess risk of death to landmark	[redacted]	0.353	0.000	Dominant	[redacted]
19% excess risk of death to landmark	[redacted]	0.349	0.000	Dominant	[redacted]
OS and PFS scenarios					
OS distribution – No Treatment effect Exponential	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Generalised Gamma	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Gompertz	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution –	[redacted]	0.365	0.000	Dominant	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
No Treatment effect Log-logistic					
OS distribution – No Treatment effect Log-normal	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Weibull	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Hazard Spline (1 knot)	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Hazard Spline (2 knots)	[redacted]	0.366	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Hazard Spline (3 knots)	[redacted]	0.366	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Odds Spline (1 knot)	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Odds Spline (2 knots)	[redacted]	0.366	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Odds Spline (3 knots)	[redacted]	0.366	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Probit Spline (1 knot)	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Probit Spline (2 knots)	[redacted]	0.365	0.000	Dominant	[redacted]
OS distribution – No Treatment effect Probit Spline (3 knots)	[redacted]	0.365	0.000	Dominant	[redacted]
PFS -Independent Models Exponential	[redacted]	0.314	0.000	Dominant	[redacted]
PFS -Independent Models Generalised Gamma	[redacted]	0.264	0.000	Dominant	[redacted]
PFS -Independent Models Gompertz	[redacted]	0.160	0.000	Dominant	[redacted]
PFS -Independent Models Log-logistic	[redacted]	0.365	0.000	Dominant	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
PFS -Independent Models Log-normal	[redacted]	0.360	0.000	Dominant	[redacted]
PFS -Independent Models Weibull	[redacted]	0.389	0.000	Dominant	[redacted]
PFS -Independent Models Hazard Spline (1 knot)	[redacted]	0.336	0.000	Dominant	[redacted]
PFS -Independent Models Hazard Spline (2 knots)	[redacted]	0.069	0.000	Dominant	[redacted]
PFS -Independent Models Hazard Spline (3 knots)	[redacted]	0.089	0.000	Dominant	[redacted]
PFS -Independent Models Odds Spline (1 knot)	[redacted]	0.344	0.000	Dominant	[redacted]
PFS -Independent Models Odds Spline (2 knots)	[redacted]	0.113	0.000	Dominant	[redacted]
PFS -Independent Models Odds Spline (3 knots)	[redacted]	0.129	0.000	Dominant	[redacted]
PFS -Dependent Models Exponential	[redacted]	0.306	0.000	Dominant	[redacted]
PFS -Dependent Models Generalised Gamma	[redacted]	0.228	0.000	Dominant	[redacted]
PFS -Dependent Models Gompertz	[redacted]	0.102	0.000	Dominant	[redacted]
PFS -Dependent Models Log-logistic	[redacted]	0.217	0.000	Dominant	[redacted]
PFS -Dependent Models Log-normal	[redacted]	0.194	0.000	Dominant	[redacted]
PFS -Dependent Models Weibull	[redacted]	0.229	0.000	Dominant	[redacted]
PFS -Dependent Models Hazard Spline (1 knot)	[redacted]	0.200	0.000	Dominant	[redacted]
PFS -Dependent Models Hazard Spline (2 knots)	[redacted]	0.275	0.000	Dominant	[redacted]
PFS -Dependent Models Hazard Spline (3 knots)	[redacted]	0.297	0.000	Dominant	[redacted]
PFS -Dependent Models Odds Spline (1 knot)	[redacted]	0.194	0.000	Dominant	[redacted]
PFS -Dependent Models Odds Spline (2 knots)	[redacted]	0.220	0.000	Dominant	[redacted]
PFS -Dependent Models Odds Spline (3 knots)	[redacted]	0.238	0.000	Dominant	[redacted]
PFS -Dependent Models Probit Spline (1 knot)	[redacted]	N/A	N/A	N/A	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
PFS -Dependent Models Probit Spline (2 knots)	[redacted]	0.181	0.000	Dominant	[redacted]
PFS -Dependent Models Probit Spline (3 knots)	[redacted]	0.199	0.000	Dominant	[redacted]
Extreme scenario: Using lowest NMB generated from the curves above: PFS -Independent Models Hazard Spline (2 knots) (NMB = 209,772) OS distribution – No Treatment effect Generalised Gamma (NMB = 227,530)	[redacted]	0.069	0.000	Dominant	[redacted]

Abbreviations: ERG: Evidence Review Group; GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LY: life year; NMA: network meta-analysis; NMB: net monetary benefit; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALY: quality-adjusted life-year; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.

Del(17p)/*TP53* mutation population (VenG versus ibrutinib)

All scenarios from Table 69 were applied (excluding the CLL11, RESONATE and Warwick ERG NMA scenarios for OS estimates) along with assessment of an additional hazard ratio from the naïve comparisons:

- Ahn. et al study (see Section B.2.9)
- Assuming equal treatment effect

Using the Ahn et al.[71] as a source of ibrutinib efficacy results in ibrutinib accruing higher QALYs and higher costs compared to VenG. This can be translated into VenG being a less effective and far less costly treatment option but still cost-effective, as per NMB values generated, for those del(17p) UK patients with limited treatments available. Moreover, on seeking advice from UK clinicians, the complete paucity of evidence for 1L CLL ibrutinib use in this population was stressed. The advice received was that no reliable conclusions can be drawn on the long-term efficacy of VenG vs ibrutinib and therefore a scenario of equivalent efficacy should be considered to enable decision making on the cost effectiveness of VenG vs ibrutinib monotherapy in the del(17p)/TP53 mutation population.

Table 71: Scenario analysis for del(17p)/*TP53* mutation population

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
Base case (Mato HR)	[redacted]	0.036	0.119	Dominant	[redacted]
HR (Ahn study)	[redacted]	-0.988	-2.201	[redacted]	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
Equal efficacy PFS HR = 1 OS HR = 1 AE disutility = 0	[redacted]	0.000	0.000	Dominant	[redacted]
Discount rate. Costs: 0%, QALYs: 0%	[redacted]	0.054	0.119	Dominant	[redacted]
Discount rate. Costs: 0%, QALYs: 6%	[redacted]	0.028	0.119	Dominant	[redacted]
Discount rate. Costs: 6%, QALYs: 6%	[redacted]	0.028	0.119	Dominant	[redacted]
Discount rate. Costs: 6%, QALYs: 0%	[redacted]	0.054	0.119	Dominant	[redacted]
Time horizon: 5 year	[redacted]	0.000	0.029	Dominant	[redacted]
Time horizon: 10 year	[redacted]	0.018	0.068	Dominant	[redacted]
Time horizon: 15 year	[redacted]	0.029	0.094	Dominant	[redacted]
Time horizon: 25 year	[redacted]	0.036	0.116	Dominant	[redacted]
TLS prophylaxis cost halved	[redacted]	0.036	0.119	Dominant	[redacted]
TLS prophylaxis cost doubled	[redacted]	0.036	0.119	Dominant	[redacted]
TLS prophylaxis cost removed	[redacted]	0.036	0.119	Dominant	[redacted]
Adverse event rates halved	[redacted]	0.038	0.119	Dominant	[redacted]
Adverse event rates doubled	[redacted]	0.034	0.119	Dominant	[redacted]
Adverse events removed	[redacted]	0.039	0.119	Dominant	[redacted]
Utility (from CLL14 trial) Pre-progression utility = 0.829	[redacted]	0.013	0.119	Dominant	[redacted]
Utility from Venetoclax monotherapy submission (pre-progression utility = 0.748; EQ-5D data study 116)	[redacted]	0.025	0.119	Dominant	[redacted]
Ibrutinib arm using utility value from TA343 for Progression-free survival under oral treatment (0.71)	[redacted]	0.031	0.119	Dominant	[redacted]
Wastage Cost Removed	[redacted]	N/A	N/A	N/A	[redacted]
PFS -Independent Models	[redacted]	-0.007	0.119	[redacted]	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
Exponential					
PFS -Independent Models Generalised Gamma	[redacted]	0.028	0.119	Dominant	[redacted]
PFS -Independent Models Gompertz	[redacted]	0.025	0.119	Dominant	[redacted]
PFS -Independent Models Log-logistic	[redacted]	0.036	0.119	Dominant	[redacted]
PFS -Independent Models Log-normal	[redacted]	0.041	0.119	Dominant	[redacted]
PFS -Independent Models Weibull	[redacted]	-0.005	0.119	[redacted]	[redacted]
PFS -Independent Models Hazard Spline (1 knot)	[redacted]	0.008	0.119	Dominant	[redacted]
PFS -Independent Models Hazard Spline (2 knots)	[redacted]	0.026	0.119	Dominant	[redacted]
PFS -Independent Models Hazard Spline (3 knots)	[redacted]	0.024	0.119	Dominant	[redacted]
PFS -Independent Models Odds Spline (1 knot)	[redacted]	0.025	0.119	Dominant	[redacted]
PFS -Independent Models Odds Spline (2 knots)	[redacted]	-0.002	0.119	[redacted]	[redacted]
PFS -Independent Models Odds Spline (3 knots)	[redacted]	-0.001	0.119	[redacted]	[redacted]
PFS -Independent Models Probit Spline (1 knot)	[redacted]	0.039	0.119	Dominant	[redacted]
PFS -Independent Models Probit Spline (2 knots)	[redacted]	-0.005	0.119	[redacted]	[redacted]
PFS -Independent Models Probit Spline (3 knots)	[redacted]	0.000	0.119	Dominant	[redacted]
PFS -Dependent Models Exponential	[redacted]	0.012	0.119	Dominant	[redacted]
PFS -Dependent Models Generalised Gamma	[redacted]	0.017	0.119	Dominant	[redacted]
PFS -Dependent Models Gompertz	[redacted]	0.032	0.119	Dominant	[redacted]
PFS -Dependent Models Log-logistic	[redacted]	-0.003	0.119	[redacted]	[redacted]
PFS -Dependent Models Log-normal	[redacted]	0.002	0.119	Dominant	[redacted]
PFS -Dependent Models Weibull	[redacted]	0.017	0.119	Dominant	[redacted]
PFS -Dependent Models Hazard Spline (1 knot)	[redacted]	0.021	0.119	Dominant	[redacted]
PFS -Dependent Models Hazard Spline (2 knots)	[redacted]	0.011	0.119	Dominant	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
PFS -Dependent Models Hazard Spline (3 knots)	[redacted]	0.008	0.119	Dominant	[redacted]
PFS -Dependent Models Odds Spline (1 knot)	[redacted]	-0.004	0.119	[redacted]	[redacted]
PFS -Dependent Models Odds Spline (2 knots)	[redacted]	-0.001	0.119	[redacted]	[redacted]
PFS -Dependent Models Odds Spline (3 knots)	[redacted]	0.005	0.119	Dominant	[redacted]
PFS -Dependent Models Probit Spline (1 knot)	[redacted]	N/A	N/A	N/A	[redacted]
PFS -Dependent Models Probit Spline (2 knots)	[redacted]	-0.009	0.119	[redacted]	[redacted]
PFS -Dependent Models Probit Spline (3 knots)	[redacted]	0.002	0.119	Dominant	[redacted]
OS distribution – Treatment effect Generalised Gamma	[redacted]	0.004	0.191	Dominant	[redacted]
OS distribution – Treatment effect Gompertz	[redacted]	0.025	0.077	Dominant	[redacted]
OS distribution – Treatment effect Log-logistic	[redacted]	0.011	0.171	Dominant	[redacted]
OS distribution – Treatment effect Log-normal	[redacted]	0.004	0.184	Dominant	[redacted]
OS distribution – Treatment effect Weibull	[redacted]	0.036	0.120	Dominant	[redacted]
OS distribution – Treatment effect Hazard Spline (1 knot)	[redacted]	0.036	0.118	Dominant	[redacted]
OS distribution – Treatment effect Hazard Spline (2 knots)	[redacted]	0.027	0.073	Dominant	[redacted]
OS distribution – Treatment effect Hazard Spline (3 knots)	[redacted]	0.026	0.071	Dominant	[redacted]
OS distribution – Treatment effect Odds Spline (1 knot)	[redacted]	0.015	0.170	Dominant	[redacted]
OS distribution – Treatment effect Odds Spline (2 knots)	[redacted]	0.050	0.146	Dominant	[redacted]
OS distribution – Treatment effect Odds Spline (3 knots)	[redacted]	0.050	0.144	Dominant	[redacted]

	List price				
	Incremental costs	Incremental QALYs	Incremental LY	ICER	NMB
OS distribution – Treatment effect Probit Spline (1 knot)	[redacted]	0.002	0.182	Dominant	[redacted]
OS distribution – Treatment effect Probit Spline (2 knots)	[redacted]	0.024	0.163	Dominant	[redacted]
OS distribution – Treatment effect Probit Spline (3 knots)	[redacted]	0.029	0.161	Dominant	[redacted]
Extreme value testing using lower HR bounds from Mato calculation (PFS HR = 0.293 and OS HR = 0.334; VenG least effective eventuality)	[redacted]	-2.906	-6.825	[redacted]	[redacted]
Extreme scenario: OS distribution – Treatment effect Generalised Gamma (NMB = £47,684) **PFS -Independent Models Generalised Gamma (NMB: 77,527)**	[redacted]	0.041	0.191	[redacted]	[redacted]
Subsequent treatment scenario 2	[redacted]	0.036	]0.119	Dominant	[redacted]
Subsequent treatment scenario 2a (50% VenR and 50% Vmono)	[redacted]	0.036	0.119	Dominant	[redacted]

Abbreviations: ERG: Evidence Review Group; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LY: life year; NMA: network meta-analysis; NMB: net monetary benefit; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALY: quality-adjusted life-year; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.

B.3.8.4 Summary of sensitivity analyses results

The base case average probabilistic ICER is closely aligned with the base case deterministic ICER for both populations. At the £30,000/QALY willingness to pay threshold typically applied in NICE appraisals, VenG was found to have a greater than 90% probability of being the cost-effective option in the base case, in both the non-del(17p)/*TP53* and del(17p)/*TP53* populations.

The scenario analysis demonstrated that VenG is consistently cost-effective when compared to GClb or ibrutinib, with all but one scenario in each population (5-year time horizon for non-del(17p)/*TP53* mutation; and extreme OS and PFS results for del(17p)/*TP53* mutation) resulting in a positive net monetary benefit.

B.3.9 *Subgroup analysis*

The subgroup of patients with del(17p)/*TP53* mutation has been considered as a distinct population, compared to patients without del(17p)/*TP53* mutation. As such, the results for this group have been presented in Sections B.3.6 and B.3.8.

No further subgroups were considered for this submission.

B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

To ensure that the model was scientifically and clinically valid, four key steps were taken. Firstly, following finalisation of the model specification, AbbVie organised an advisory board where the model structure, key model assumptions, and associated inputs were discussed in detail with experienced clinicians in the CLL space and health economists. Secondly, two consultants familiar with the model used for relapsed/refractory CLL conducted a complete quality check of the model using a pre-specified model QC template. Thirdly, two health-economic experts reviewed the model and its underlying assumptions. Following their review, the model was updated and the model challenges with regards to the OS predictions beyond the CLL14 trial period were presented to a leading CLL clinician involved with the CLL trials. Lastly, following on from the health economic expert validation of the final model, two clinical experts who had previously participated in the advisory board provided their expert opinion based on clinical practice on the model outcomes to help test the external validity of the model extrapolations.

B.3.10.2 Advisory board meeting

Based on the outcomes of the advisory board, key structural changes were made, in particular surrounding the methods for extrapolating OS.

The following key advice from the advisory board was implemented in the model:

- Use of a partitioned survival model structure to model previously untreated CLL patients
- When choosing the extrapolation approach to consider evidence on long-term outcomes from sources beyond the pivotal trial
    - To take this suggestion into consideration, a targeted review was conducted to identify recent and relevant clinical trials which could be used to validate the long-term outcomes from the model. The CLL11 trial was identified as the key data source of interest since the trial was specific to the patient population of interest and also specific to the treatment arms of interest. The CLL11 trial provided 5 years of follow up data
    - To help make use of the data from the CLL11 trial, an approach previously adopted in an accepted recent technological appraisal (TA343) was adopted.[67] This approach involved use of the PPS period

Furthermore, the following model parameters were validated during the ad-board:

- Resource use and costs validation:

    - Frequency and categories of resource use for pre and post-progression
    - Addition of resource use categories not previously included for pre and post-progression
- Adverse event cost validation
    - Update of cost of treating one episode of adverse event
- Utility and disutility validation
    - Update of disutilities and duration of adverse events
- Practice level usage of standard IV versus rapid IV versus subcutaneous for rituximab (used in the subsequent treatment mix).
- Practice level usage of standard IV versus rapid IV for obinutuzumab.
- For the indirect comparison sources versus ibrutinib in the del(17p)/*TP53* population, two papers were recommended which were reporting on the same trial.[71, 72] These were further taken into consideration during the network meta-analysis feasibility assessment

Based on the advice received the following steps were taken:

1. A targeted review was conducted to identify recent and relevant trials for the patient population most aligned with the CLL14 trial with longer follow-up data. Based on the targeted review the CLL11 trial was the trial with the most recent and relevant patient population of interest with 5 year follow up data. Therefore, the CLL11 trial data was used to further validate the results from the CLL14 extrapolations.
2. Resource use, cost, adverse event cost, disutility inputs were updated based on the recommendations received from the advisory board.

B.3.10.3 Independent health economic expert validation

One expert identified two key internal minor issues with the model which did not significantly alter the final results. These issues were the subsequent treatment cost calculation for venetoclax monotherapy and the use of age-adjusted utility. These two issues were addressed in the final version of the model.

In addition, the model formulas were simplified where possible without compromising the structural integrity of the model.

Another expert did not identify any programming issues with the model. However, their comments surrounding the time to event modelling methodology were taken into consideration.

B.3.10.4 Clinician expert validations

Based on advice from clinical experts, it was decided to select the log-logistic distribution as the base case for the independent models for each treatment arm for the PFS.

In addition, the subsequent treatment line was informed by the suggestions of the clinical validations.

An excess mortality risk due to infections in previously untreated CLL patients following progression were highlighted with the clinicians and this has been explored within a scenario.

Finally, all three clinicians agreed that the CLL11 follow-up trial data would not reflect the innovative treatment regimens provided to subsequent treatment line patients in the previously untreated patient population. Therefore, the overall survival rates seen from the CLL11 trial are much lower compared to the CLL14 trial.

B.3.11 *Interpretation and conclusions of economic evidence*

B.3.11.1 Strengths of the analysis

For the non-del(17p)/*TP53* population, the best source of evidence for the VenG arm and the GClb arm was the CLL14 trial which includes the main comparator of prime relevance to the NHS in England and Wales. The choice of survival models and distributions to extrapolate beyond the trial period was made using validation from the recent external evidence for the comparable patient population to CLL14 (the CLL11 trial). The results were validated by clinical experts within the field of CLL while the health economic model was validated by two health economic experts. Finally, the CLL14 trial is considered a well-conducted RCT with low risk of bias and is therefore a robust source of evidence to inform the economic evaluation of this decision problem.

B.3.11.2 Limitations and interpretation of clinical evidence

Demonstrating robust evidence about the long-term cost-effectiveness of VenG for the treatment of previously untreated CLL patients is challenging for two reasons. Firstly, the CLL14 trial data are immature; the median OS, PFS, and TTNT has not yet been reached. And secondly, there is a lack of available data from the comparator studies for the comparison of ibrutinib vs VenG for the del(17p)/*TP53* population.

When the patterns observed in the CLL14 data are extrapolated, OS ends up being close to background mortality since the OS curve is constrained to the hazards of background mortality. Given that the CLL patients are older than 70 years of age and previously untreated patients are healthier than relapsed and refractory patients, their likelihood of dying from other causes when on treatment (i.e., reasons captured within background mortality) is probable and is supported by clinical expert opinion.

In the absence of mature data from the CLL14 patient population, long-term OS results are uncertain. To enable validation of the extrapolated results from the CLL14 patient population, external evidence was used. Namely, the 5-year follow-up data from the CLL11 trial (as suggested within the UK advisory board) was incorporated within a scenario. The CLL11 serves as a pessimistic scenario since the post-progression period covered a time with limited innovative treatment regimens, in contrast to those available more recently during the CLL14 trial. Therefore, the OS estimates are underestimated and poorly fit the VenG as well as the GClb treatment arms. The post-progression period from a relapsed and refractory patient population were also applied within the model. The MURANO population and the ibrutinib patients generated from the Warwick ERG NMA resulted in the OS curve in the model hitting background mortality, since these patients were 10 years younger with better survival rates than the CLL14 trial population. The ibrutinib arm from the RESONATE trial underestimated the OS

curve for the CLL14 trial since considerably more patients in the RESONATE trial had the del(17p)/*TP53* genetic mutation adversely affecting survival outcomes. Therefore, the CLL14 trial, although with immature OS data, provides the closest estimates for the patient population being modelled.

B.3.11.3 Conclusions

Previously untreated FCR/BR-unsuitable CLL patients without del(17p)/*TP53* mutation receiving VenG are estimated to incur costs of £[redacted] and to accrue 6.837 QALYs, at list price, over a 30-year time horizon (£[redacted] and 6.837 QALYs at venetoclax PAS price). GClb is estimated to incur higher costs and due to the faster disease progression to accrue fewer QALYs and is therefore dominated by VenG. Probabilistic analysis shows that at a willingness to pay of approximately £30,000, VenG has over [redacted] probability of being the most cost-effective treatment. For the population of patients with del(17p)/*TP53* mutation, VenG is estimated to incur costs of £[redacted] and accrue 2.991 QALYs, at list price, over a 30-year time horizon (£[redacted] and 2.991 QALYs at venetoclax PAS price). Ibrutinib is estimated to accrue fewer QALYs and incur higher cost and is therefore dominated by VenG.

As such, VenG represents the dominant and cost-effective option for the NHS across both populations considered within this appraisal.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

ADDENDUM to

Company evidence submission

February 2020

File name	Version	Contains confidential information	Date
NICE VenG for CLL Addendum	Final	Yes	14th February 2020

Contents

Tables

Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
BR	Bendamustine with rituximab
CI	Confidence Interval
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CRi	Complete response with incomplete bone marrow recovery
EOT	End-of-treatment
EQ-5D	European Quality of Life 5 Dimensions
ERG	Evidence Review Group
FCR	Fludarabine, cyclophosphamide and rituximab
FUM	Follow-up month
GClb	Chlorambucil with obinutuzumab
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
LYG	Life years gained
MRD	Minimal residual disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression-free survival
PPS	Post-progression survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SAE	Serious adverse event
TLS	Tumour lysis syndrome
ToT	Time on treatment
TTNT	Time to next treatment
uMRD	Undetectable minimal residual disease
VenG	Venetoclax with obinutuzumab
WTP	Willingness-to-pay

A.1 Background

The company evidence submission (Documents A and B and an economic model) was made to NICE on 29th October 2019. That submission was based on the August 2018 data cut-off of the CLL14 trial: 28.1 months median follow-up time from randomisation, i.e. roughly one year off-treatment (measured as last study treatment day to last day known to be alive). This addendum to the company submission includes results from the August 2019 data cut-off of the CLL14 trial: 39.6 months median follow-up time from randomisation, i.e. approximately two years off-treatment. This addendum to the company evidence submission is accompanied by a revised economic model

Since the original submission, the Committee for Medicinal Products for Human Use of the European Medicines Agency granted positive opinion on 31st January 2020 for the following indication: venetoclax in combination with obinutuzumab (VenG) is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). Marketing authorisation is anticipated in March 2020.

As with the original company evidence submission, two subpopulations, consistent with the NICE final scope, are considered in this addendum (Table 1).

Table 1: Sub-populations considered in this addendum

Population	Comparison	Rationale
Subpopulation 1: Patients with previously untreated CLL, without del(17p)/*TP53* mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR	VenG vs GClb	• This subpopulation best reflects the cohort of the pivotal trial, CLL14 • This subpopulation is consistent with NHS clinical practice; clinical experts treating patients with CLL in the UK NHS have confirmed that VenG would not be used in patients suitable for fludarabine- or bendamustine-based therapies
Subpopulation 2: Patients with previously untreated CLL, with del(17p)/*TP53* mutation	VenG vs ibrutinib monotherapy	• This subpopulation is also reflected in the pivotal trial, CLL14, where [redacted] of patients had the del(17p)/*TP53* mutation

Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil with obinutuzumab; NHS: National Health Service; VenG: venetoclax with obinutuzumab.

Table 2 summarises the key updates to the initial submission included in this addendum.

Table 2: Key updates included in this addendum

Clinical section	Economic section
Updates based on the August 2019 data cut-off have been made to the following: • Patient disposition • Investigator-assessed PFS • MRD • OS • Duration of response • EFS • TTNT • Subgroup analyses • Unadjusted naïve indirect comparison • AEs	The key changes made to the economic model are as follows: • Update of all survival analyses for modelled outcomes (PFS, OS, TTNT) using individual patient level data from the August 2019 data cut-off • Update of CLL14 patient allocation, and corresponding baseline information, to either of the two modelled populations (with del(17p)/*TP53* mutation or without) • Update of HRs as generated from the naïve comparison to ibrutinib data from relevant literature sources (changes only apply to the del(17p)/*TP53* mutation model population)[1, 2] • Update of the time-on-treatment information as per the August 2019 data cut-off • Update of modelled serious treatment-emergent AEs, which had an incidence of ≥1% in the key trial arms for each included treatment

Changes made to the economic model apply to both modelled populations, del(17p)/*TP53* and non-del(17p)/*TP53*, unless stated otherwise.
Abbreviations: AEs: adverse events; EFS: event-free survival; HRs: hazard ratios; MRD: minimal residual disease; OS: overall survival; PFS: progression-free survival; TTNT: time-to-next treatment.

Overall, with longer follow-up off-treatment, compelling efficacy results continue to be observed with VenG, in addition to a safety profile that continues to be manageable, predictable and consistent with the known safety profile of both agents.

The updated economic analyses demonstrate that, at list price, VenG dominates relevant comparators and is cost-effective at the threshold of £20,000–£30,000 per QALY gained in both the del(17p)/*TP53* and non-del(17p)/*TP53* mutation populations. The probabilistic results are broadly in line with the deterministic results showing that VenG is dominant versus both chlorambucil with obinutuzumab (GClb) and ibrutinib.

In conclusion, the evidence presented in this addendum suggests that VenG can increase the range of effective treatment options available to treat CLL in both patients with and without del(17p)/*TP53* mutation, providing a valuable alternative to current first-line treatment options. Furthermore, VenG has the potential to provide substantial health-related benefits in the form of a fixed-duration chemotherapy-free treatment, with a manageable side effect profile. This enables a significant proportion of patients to experience prolonged times without therapy, reducing the overall cost burden of treatment.

A.2 Clinical effectiveness

A.2.1 *Overview of results*

At the latest data cut-off (August 2019) of the CLL14 trial, the median follow-up time from randomisation was 39.6 months and the median duration of off-treatment follow-up (i.e. last study treatment day to last day known to be alive) was 29.3 months. Please note that the August 2019 data cut-off only includes investigator assessed outcomes. In addition, overall response and complete response (CR), which were presented as part of the initial submission to NICE, were only assessed at end of treatment, and as such are not included in the updated data cut or economic evaluation and are therefore not presented in this addendum.

A comparison of the key results from the CLL14 August 2018 data cut-off versus the August 2019 data cut-off is presented in Table 3. Based on the August 2019 data cut-off, compelling efficacy results continue to be observed with VenG, in addition to a safety profile that continues to be manageable, predictable and consistent with the known safety profile of both agents. The median progression-free survival (PFS) in the VenG arm was not reached ([redacted] events of progression or death in 216 patients; [redacted]). The median PFS in the GClb arm was 35.6 months ([redacted] events in 216 patients; [redacted]; 95% confidence interval [CI]: [redacted]). The risk of disease progression or death was reduced by 69% (stratified hazard ratio [HR] 0.31; 95% CI: 0.22, 0.44; descriptive p<0.001) for patients in the VenG arm; this observed risk reduction is consistent with the observation at the time of the primary cut-off date (August 2018; Table 3). The Kaplan–Meier estimates for PFS at 3 years (36 months) post-randomisation remained high in the VenG arm (81.9%) compared to the GClb arm (49.5%).

The median overall survival (OS) was not reached in either arm: [redacted] patients ([redacted]) in each treatment arm had died. There was no evidence of a difference in OS between arms (HR 1.03; 95% CI: 0.60, 1.75; p=0.92). Interestingly, the number of patients who went on to receive second-line treatments after disease progression was nearly [redacted] in the GClb arm ([redacted] patients [[redacted]]) than in the VenG arm ([redacted] patients [[redacted]]). The most common second-line treatment received was [redacted].

Table 3: Summary of results from the CLL14 trial

	August 2018 data cut (28.1 months median follow-up)		August 2019 data cut (39.6 months median follow-up)	
	VenG (N=216)	GClb (N=216)	VenG (N=216)	GClb (N=216)
Investigator-assessed PFS				
Median PFS, months (95% CI)	Not reached	Not reached	Not reached	35.6 ([redacted])
Events, n (%)	30 (13.9)	77 (35.6)	[redacted]	[redacted]
Stratified analysis, HR (95% CI)	0.35 (0.23, 0.53; p<0.0001)		0.31 (0.22, 0.44; descriptive p<0.001)	
Kaplan–Meier estimate at 2 years (24 months), %	88.2	64.1		
Kaplan–Meier estimate at 3 years (36 months), %			[redacted]	[redacted]
OS				
Median OS, months (95% CI)	Not reached	Not reached	Not reached	Not reached
Deaths, n (%)	20 (9.4)	17 (8.0)	[redacted]	[redacted]
Stratified analysis, HR (95% CI)	1.24 (0.64, 2.40; p=0.5216)		1.03 (0.60, 1.75; p=0.92)	
uMRD	**3 months after treatment completion**		**18 months after treatment completion**	
Peripheral blood, %	75.5	35.2	47.2	7.4
Difference in uMRD in peripheral blood, % (95% CI)	40.3 (31.5, 49.1; p<0.0001)		39.8 [redacted]	
Bone marrow, %	56.9	17.1	No bone marrow samples collected at 18 months	
Difference in uMRD in bone marrow, % (95% CI)	39.8 (31.3, 48.4; p<0.0001)			
CRR	**3 months after treatment completion**			
CR, n (%)	99 (45.8)	47 (21.8)	These data were only collected at the EOT assessment	
CRi, n (%)	7 (3.2)	3 (1.4)		
Combined response (CR+CRi), n (%)	107 (49.5)	50 (23.1)		
Difference in CRR, % (95% CI)	26.4 (17.4, 35.4; p<0.0001)			

Abbreviations: CI: confidence interval; CR: complete response; CRi: complete response with incomplete bone marrow recovery; CRR: complete response rate; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; PFS: progression-free survival; uMRD: undetectable minimal residual disease; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Primary Clinical Study Report)[3] (August 2018 data cut: 28.1 months follow-up); AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.2 *Patient Disposition*

A full consort diagram of the study population flow is provided in Figure 1.

Figure 1: Patient disposition at the August 2019 clinical cut-off date

Dashed lines indicate flow of patients who discontinued one or both components of treatment and subsequently entered post-treatment follow-up. In the VenG arm, death of [redacted] is recorded on the study completion/early discontinuation form only and not on the death case report form; therefore, this [redacted] is not counted in the number of deaths in the ITT or safety population. In the GClb arm, [redacted] died before study drug administration, so is included in the ITT population, but not the safety population; therefore, this [redacted] is not counted in the number of deaths in the safety population.
[a] Obinutuzumab or chlorambucil, although obinutuzumab administered first per protocol.
[b] Obinutuzumab or venetoclax, although venetoclax not scheduled until Day 22 of Cycle 1.
[c] Obinutuzumab and chlorambucil.
[d] Obinutuzumab and venetoclax.
[e] All patients who received treatment and did not discontinue the study within 30 days of last exposure were considered as having entered post-treatment follow-up.
[f] Date as of current clinical cut-off data of August 2019.
Abbreviations: GClb: chlorambucil with obinutuzumab; tx: treatment; VenG: venetoclax with obinutuzumab; w/d: withdrawal.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.3 *Investigator-assessed PFS*

As of the August 2019 clinical cut-off date, all patients had been off-treatment for a median of [redacted] (range: [redacted]) in the VenG arm and [redacted] (range: [redacted]) in the GClb arm. After a median follow-up of 39.6 months (range: [redacted]), the investigator-assessed PFS was significantly higher in patients in the VenG arm ([redacted] events in 216 patients including [redacted] with progressive disease [PD] and [redacted] deaths without PD) than in patients in the GClb arm ([redacted] events in 216 patients including [redacted] PDs and [redacted] deaths without PD; HR 0.31 [95% CI: 0.22, 0.44];

descriptive p<0.001, stratified log-rank test). The number of patients with PFS events on or after treatment is [redacted] in the VenG arm ([redacted]) when compared to the GClb arm ([redacted]) (Table 4).

Table 4: Investigator-assessed PFS results at the August 2019 clinical cut-off date

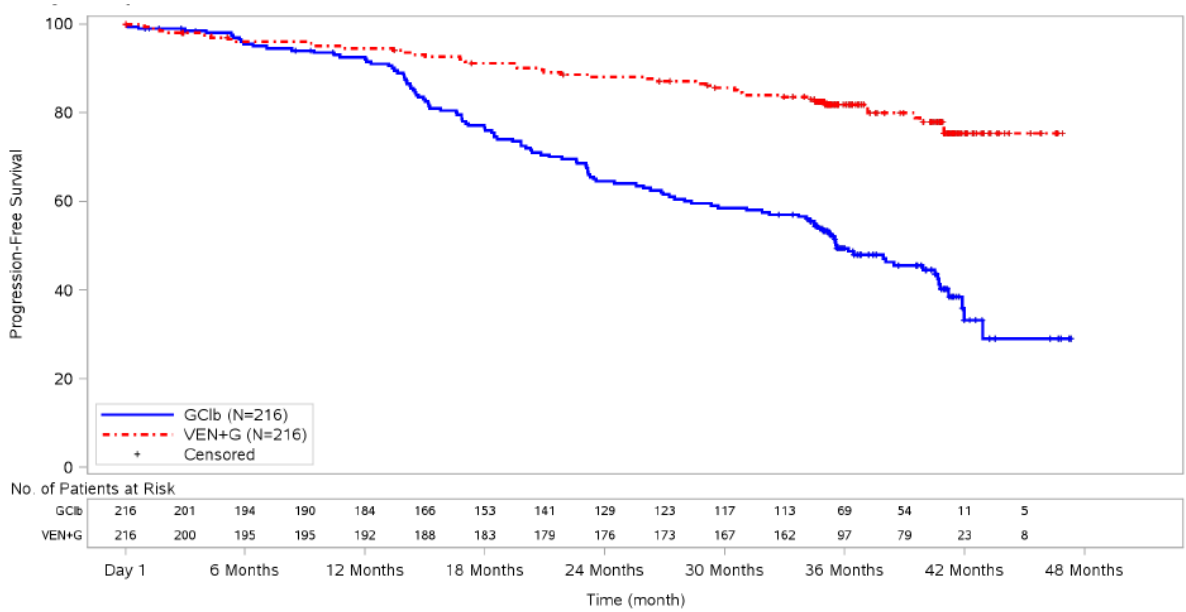
	Events, n (%)	HR (95% CI)	Stratified p value	Pre-specified IA boundary	Kaplan–Meier estimates		
					PFS 1 Year (%)	PFS 2 Year (%)	PFS 3 Year (%)
VenG (N=216)	[redacted]	0.31 (0.22, 0.44)	<0.001	p=0.0009	[redacted]	88.2	81.9
GClb (N=216)	[redacted]				[redacted]	64.1	49.5

*[redacted] PD and [redacted] deaths; †[redacted] PD and [redacted] deaths.
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; IA: interim analysis; PD: progressive disease; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

Investigator-assessed PFS results are presented in Table 4. Median PFS was 35.6 months (95% CI: [redacted]) in the GClb arm but was not reached in the VenG arm. However, the improvement seen in PFS was statistically significant and clinically meaningful. As can be seen in Table 4, a high proportion (81.9%) of patients in the VenG arm remained progression free after 36 months, compared with 49.5% of patients in the GClb arm.

The Kaplan–Meier plots show separation of the curves in favour of VenG after 6 months, which was maintained over time, based on 39.6 months follow-up (Figure 2).

Figure 2: Kaplan–Meier plot of investigator-assessed PFS

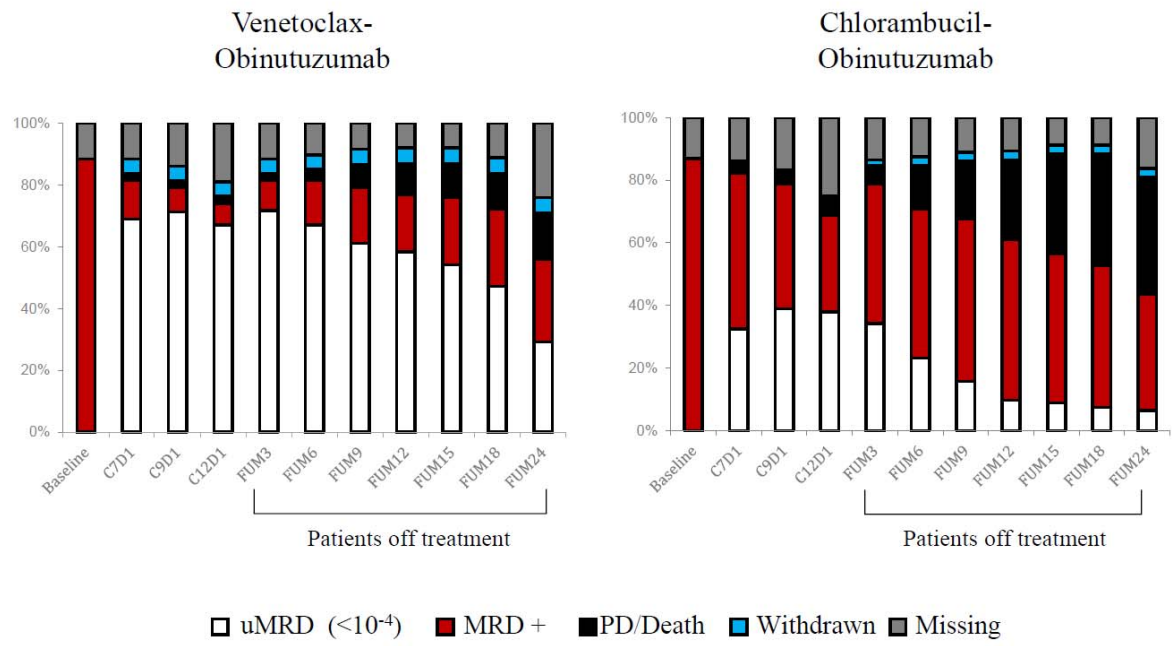


Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.4 *Minimal residual disease (MRD)*

Following EOT, no additional bone marrow samples were collected and MRD was assessed in peripheral blood every 3 months through 18 months post-treatment and then every 6 months. As of the August 2019 clinical cut-off date, undetectable MRD (uMRD) rate in peripheral blood continues to be higher in the VenG arm compared with the GClb arm (Figure 3). At the 18-month follow-up visit, uMRD in peripheral blood was 47.2% in the VenG arm and 7.4% in the GClb arm. The difference in uMRD rates was [redacted] (95% CI: [redacted]; [redacted]).

Figure 3: uMRD rates in peripheral blood over time*



Abbreviations: EOT: end-of-treatment; FUM: follow-up month; MRD: minimal residual disease; PD: progressive disease; uMRD: undetectable minimal residual disease.
*the number of missing samples increased through FUM 24
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.5 *OS*

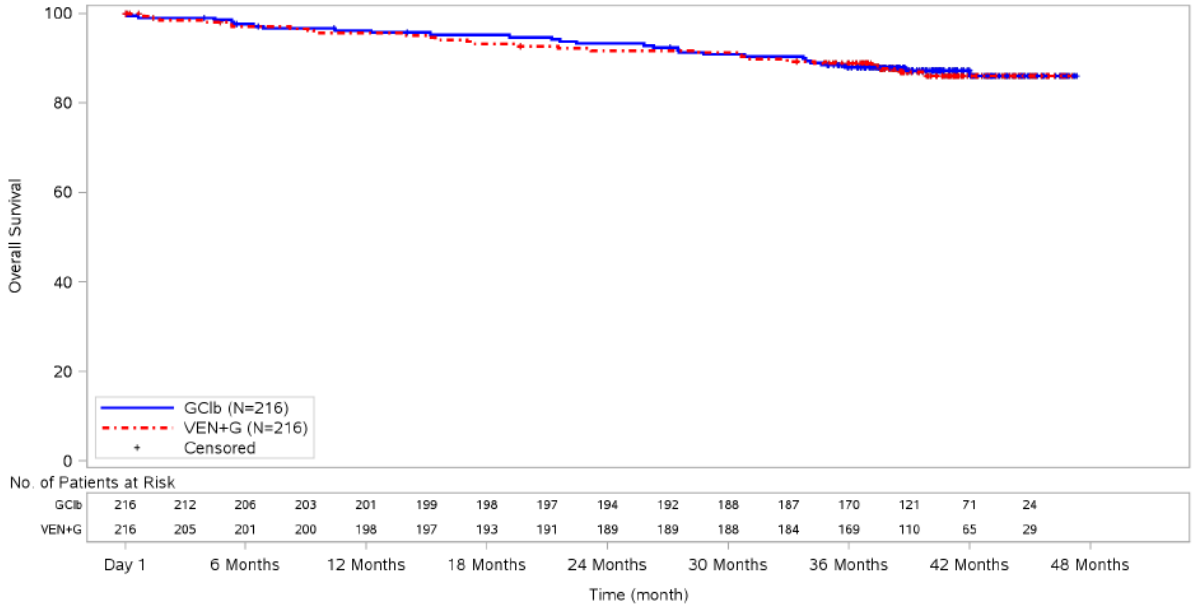
As of the August 2019 clinical cut-off date, a total of [redacted] randomised patients had died; [redacted] patients ([redacted]) in the VenG arm and [redacted] patients ([redacted]) in the GClb arm ([redacted] died prior to receiving any treatment). The median OS was not reached in either arm and there was no evidence of difference in OS between the two arms. OS results are presented in Table 5 and the corresponding Kaplan–Meier plot is provided in Figure 4.

Table 5: OS results (interim analysis) at August 2019 clinical cut-off date

	Events n (%)	HR (95% CI)	Stratified p value	Pre-specified IA boundary	Kaplan–Meier estimates		
					OS 1 Year (%)	OS 2 Year (%)	OS 3 Year (%)
VenG (N=216)	[redacted]	1.03 (0.60, 1.75)	0.92	p=0.007	[redacted]	91.8	88.9
GClb (N=216)	[redacted]				[redacted]	93.3	88.0

Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; IA: interim analysis; HR: hazard ratio; OS: overall survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

Figure 4: Kaplan–Meier plot of OS



Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.6 *Duration of response*

As of the August 2019 clinical cut-off date, duration of response was [redacted] in the VenG arm compared with the GClb arm (stratified: HR [redacted], 95% CI: [redacted]; descriptive [redacted]). The median duration of response was [redacted] in the VenG arm compared with [redacted] in the GClb arm. Kaplan–Meier estimates for duration of response were [redacted] and [redacted] at 36 months in the VenG and GClb arms, respectively.

The Kaplan–Meier plots showed [redacted], which was maintained over time (Figure 5).

Figure 5: Kaplan–Meier plot of duration of response

Abbreviations: GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.7 *Event-free survival (EFS)*

As of the August 2019 clinical cut-off date, the median EFS was [redacted] in the VenG arm compared with [redacted] in the GClb arm. Patients treated with VenG show [redacted] duration of EFS and [redacted] risk of having an EFS event (progression, death or start of new anti-CLL therapy) than GClb (stratified: HR [redacted], 95% CI: [redacted]; descriptive [redacted]).

Over time, the VenG arm showed [redacted] rates of EFS than GClb – Kaplan–Meier estimates for EFS were [redacted]% and [redacted]% at 36 months in the VenG and GClb arms, respectively.

The corresponding Kaplan–Meier plot is provided in Figure 6.

Figure 6: Kaplan–Meier plot for EFS

Abbreviations: EFS: event-free survival; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.2.8 *Time-to-next treatment (TTNT)*

As of the August 2019 clinical cut-off date, [redacted] patients in the GClb arm and [redacted] patients in the VenG arm had started a new anti-leukemic therapy or had died before initiating a new therapy. The risk of starting a new treatment was reduced in the VenG arm compared with patients in the GClb arm (stratified: HR 0.51; 95% CI: 0.34, 0.78) (Table 6).

Table 6: Summary of TTNT results at August 2019 clinical cut-off date

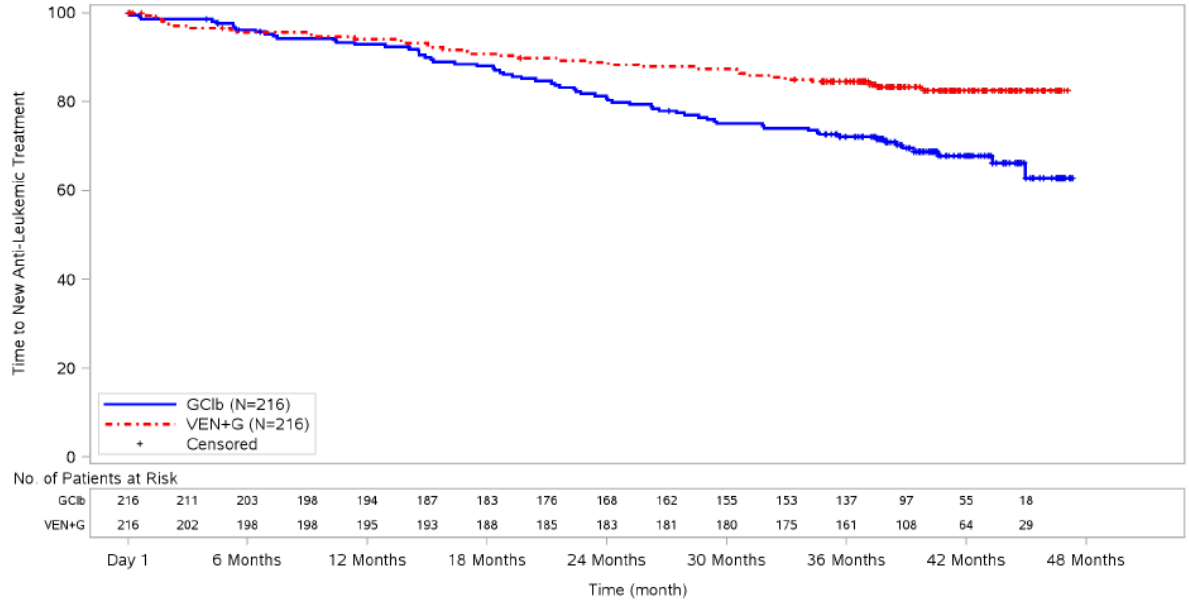
	Patients with event, n (%)	Earliest contributing event, n		HR (95% CI)
		New anti-leukemic treatment	Death*	
VenG (N=216)	[redacted]	[redacted]	[redacted]	0.51 (0.34, 0.78)
GClb (N=216)	[redacted]	[redacted]	[redacted]	

*The number of deaths recorded in this analysis is lower than the total for the August 2019 data cut because some patients had begun a new anti-CLL treatment prior to death, and it is the earliest event that counts here.
**One patient in the VenG arm, who received new antileukemic treatment was censored at Day 1 because the patient was randomised but did not receive study treatment before discontinuing from the study. The censored count is therefore [redacted], while the ITT count is [redacted].
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

The median time to new anti-CLL treatment was not reached in either treatment arms. The difference in time to new anti-CLL treatment between the VenG arm and GClb [redacted] – the time point analysis at 12 months was [redacted] in the VenG arm and [redacted] in GClb arm, [redacted] in the VenG arm and [redacted] in the GClb arm at 24 months, and 84.5% in the VenG arm and 72.2% in the GClb arm at 36 months.

The Kaplan–Meier plots showed separation of the curves in favour of VenG around 15 months, which was maintained over time (Figure 7).

Figure 7: Kaplan–Meier plot for TTNT



Abbreviations: CI: confidence interval; EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

As of the August 2019 clinical cut-off date, a [redacted] proportion of patients in the VenG arm ([redacted]) compared with the GClb arm ([redacted]) received new anti-CLL treatment after or before disease progression. [redacted] patients who received new anti-CLL treatment received it [redacted] disease progression ([redacted] of patients and [redacted] of patients in the VenG and GClb arms, respectively).

In the VenG arm, after disease progression, [redacted] patients had received ibrutinib and [redacted] patients had received other treatments; [redacted] patients have received venetoclax as new anti-CLL treatment. In the GClb arm, after disease progression, [redacted] patients had received ibrutinib alone or in combination, [redacted] patients had received venetoclax alone or in combination; the remaining treatments received by more than one patient after disease progression were bendamustine with rituximab (BR) ([redacted] patients), R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; [redacted] patients), and rituximab ([redacted] patients).

A.2.9 *Subgroup analyses*

Pre-specified subgroup analyses of the primary endpoint of investigator-assessed PFS were performed to evaluate internal consistency of the primary efficacy analysis and to determine whether baseline clinical characteristics or molecular features had an impact on the efficacy of VenG compared with GClb. Some of the included subgroups are presented in Table 7.

Table 7: Pre-planned subgroups for PFS

Variable	Comparison
Age	<75 years vs ≥75 years
Gender	Male vs female
Binet stage at screening	A, B, C
Cytogenetic subgroups	Del(17p), del(11q), trisomy 12, no abnormalities,

	del(13q)
TP53 deletion and/or mutation	Present vs not present
IGHV mutational status	Unmutated vs mutated

Abbreviations: del(11q): chromosome 11q deletion; del(13q): chromosome 13q deletion; del(17p): chromosome 17p deletion; IGHV: immunoglobulin heavy-chain variable region; PFS: progression-free survival.
Source: Fischer et al. 2019[5]

As of the August 2019 clinical cut-off date, consistent improvements in investigator-assessed PFS were observed in patients treated with VenG in major clinical and biologic subgroups including high-risk and low-risk as well as young and older patients. A summary forest plot of the investigator-assessed PFS subgroup analyses for the subgroups described in Table 7 is presented in Figure 8.

Figure 8: Investigator-assessed PFS by prognostic subgroup at August 2019 clinical cut-off date (unstratified analysis)

Abbreviations: CI: confidence interval; del(11q): chromosome 11q deletion; del(13q): chromosome 13q deletion; del(17p): chromosome 17p deletion; GClb: chlorambucil with obinutuzumab; IGHV: immunoglobulin heavy-chain variable region; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

Cytogenetic subgroups

Patients with a del(17p)/*TP53* mutation have been observed to have significantly inferior disease response, duration of response and OS on standard CLL treatments.[6, 7] As such, they are considered as high-risk patients with a significant unmet need for new treatment options. For

patients with del(17p), the primary outcome of investigator-assessed PFS for VenG compared with GClb was consistent with that of the overall trial population (HR [redacted]; 95% CI: [redacted] compared with HR [redacted]; 95% CI: [redacted]). The same was also observed for patients with *TP53* deletion and/or mutation (HR [redacted]; 95% CI: [redacted]).

As of the August 2019 clinical cut-off date, VenG statistically significantly improved investigator-assessed PFS compared with GClb, independent of immunoglobulin heavy-chain variable region (*IGHV*) mutational status (HR [redacted]; 95% CI: [redacted] in the unmutated *IGHV* subgroup compared with HR [redacted]; 95% CI: [redacted] in the mutated *IGHV* subgroup).

These results demonstrate that VenG consistently outperforms GClb, even within high-risk patient subgroups, providing clinically meaningful improvements in PFS in all populations, including those with few treatment options currently available to them.

A.2.10 *Meta-analysis and indirect and mixed treatment comparisons*

As discussed in section B.2.8 of the original submission, a meta-analysis was not feasible for the comparison of VenG and ibrutinib in the del(17p)/*TP53* mutation population. An update of the naïve indirect comparisons is presented.

A.2.10.1 Unadjusted naïve indirect comparison (Mato et al. 2018)[2]

In this section, unstratified Cox regression models were applied to estimate the relative effectiveness, in terms of PFS and OS, of VenG versus ibrutinib in CLL patients with del(17p)/*TP53* mutation, using data from the CLL14 trial (August 2019 clinical cut-off) and data from the Mato et al. publication.[2, 4] The same methodology as applied in the original submission is utilised here, with the results updated to incorporate the August 2019 clinical cut-off data.

Alignment of inclusion/exclusion criteria

A comparison is made between the Mato et al. and the CLL14 trial.[2, 4] The inclusion/exclusion criteria between the CLL14 trial and the Mato publication are not the same, patients may exist in the CLL14 who would never have been eligible to compare Mato et al., and hence may contribute bias to the results. Therefore, these patients were removed from the IPD before proceeding with the comparison process. This led to a sample size of 25 patients for the VenG arm that were naively compared to 110 patients from the Mato publication for the Ibrutinib arm

Unadjusted HR of PFS

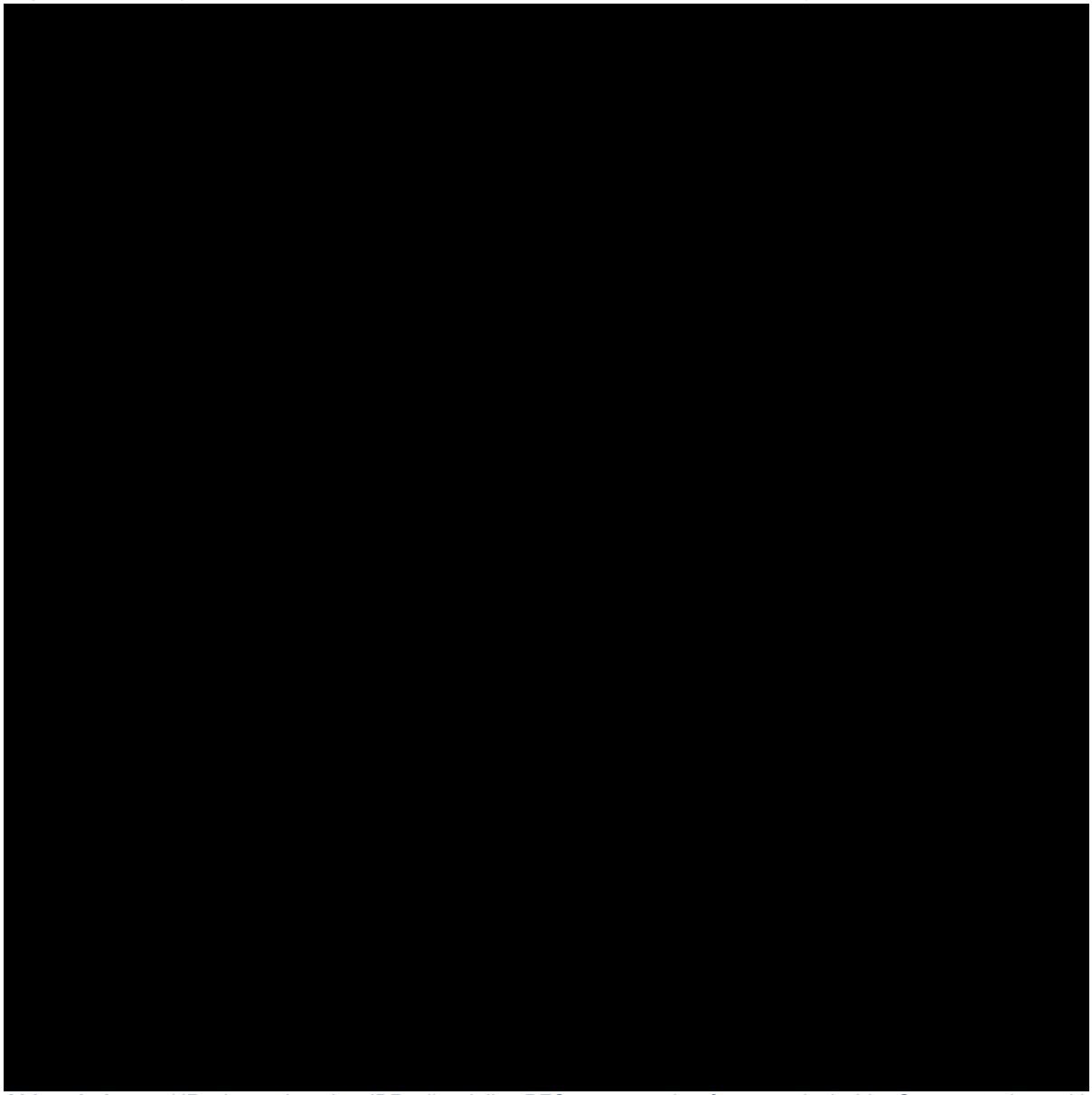
Error! Not a valid bookmark self-reference. and Figure 9 present the results for PFS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation. The naïve comparison estimates a HR of 0.660 (95% CI: 0.270, 1.615). However, the results are not statistically significant (log rank test: p=0.363) with very wide CIs, which suggest that the 'true' effect ranges from ibrutinib having superior PFS compared with VenG to VenG having superior PFS compared with ibrutinib. These key factors lead to the conclusion that the point estimate cannot be considered reliable or robust, alongside the fact that the proportional hazards assumption does not hold (curves cross; Figure 9).

Table 8: Unadjusted HR of PFS between ibrutinib (Mato et al. study) and VenG

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value
Ibrutinib (VenG reference)	0.660	0.270	1.615	0.363

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 9: Unadjusted HR of PFS between ibrutinib (Mato et al. study) and VenG (CLL14)



Abbreviations: HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Unadjusted HR of OS

Table 9 and Figure 10 present the results for OS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation. The naïve comparison estimates a HR of 0.841 (95% CI: 0.301, 2.352). However, similar to the PFS comparison, the results are not

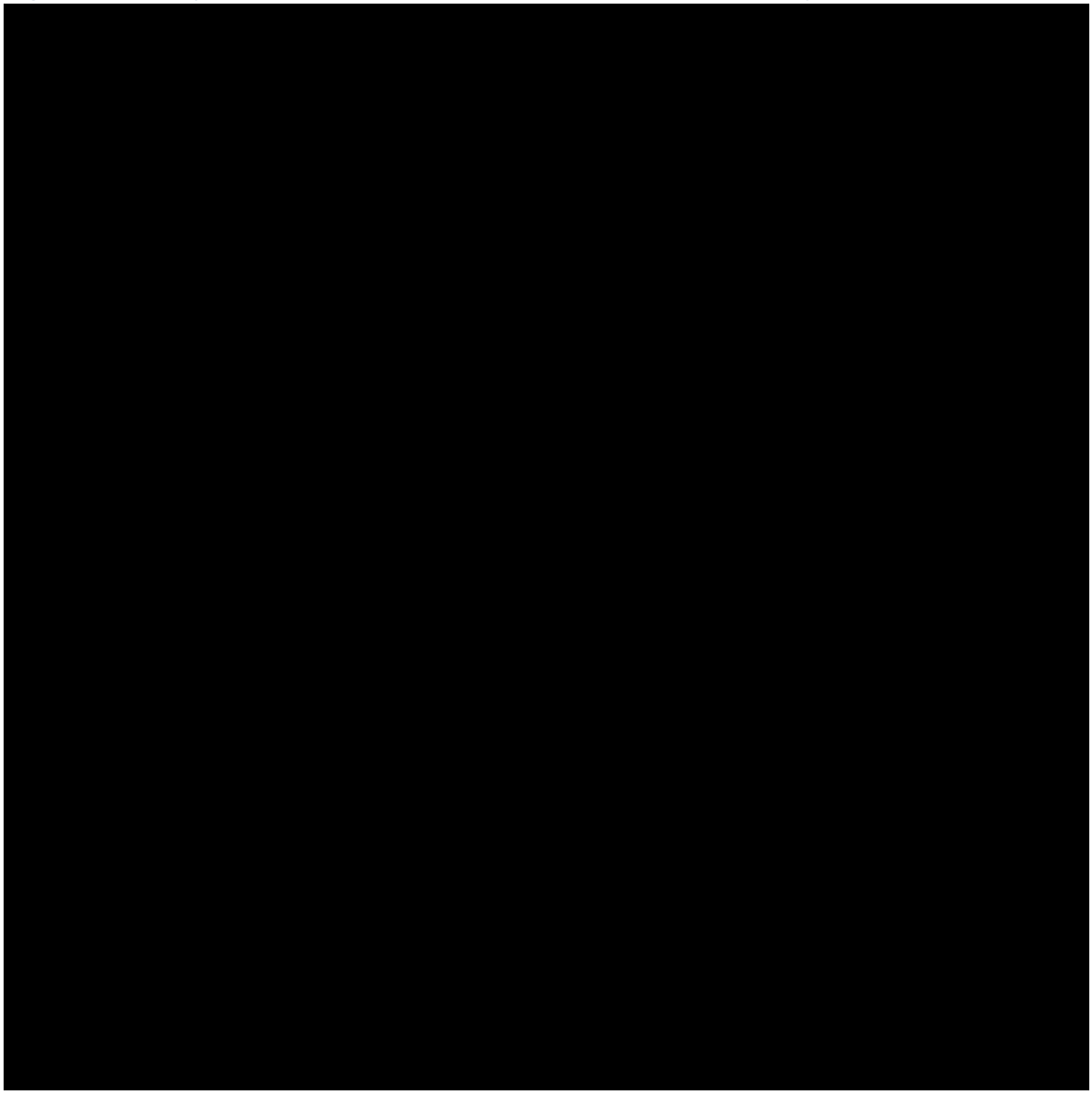
statistically significant (log rank test: p=0.741) with very wide CIs. This again indicates that the point estimate cannot be considered reliable or robust.

Table 9: Unadjusted hazard ratio of OS between ibrutinib (Mato et al. study) and VenG

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value
Ibrutinib VenG (reference)	0.841	0.301	2.352	0.741

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; VenG: venetoclax with obinutuzumab.

Figure 10: Unadjusted HR of OS between ibrutinib (Mato et al. study) and VenG



Abbreviations: HR: hazard ratio; IBR: ibrutinib; OS: overall survival; VenG: venetoclax with obinutuzumab.

A.2.10.2 Unadjusted naïve indirect comparison (Ahn et al. 2018)[1]

In this section, unstratified Cox regression models were applied to estimate the relative effectiveness, in terms of PFS and OS, of ibrutinib versus VenG in previously untreated CLL

patients with del(17p)/*TP53* mutation, using data from the CLL14 trial and Ahn et al. 2018.[1, 4] The same methodology as applied in the original submission is utilised here, with the results updated to incorporate the August 2019 clinical cut-off data.

Alignment of inclusion/exclusion criteria

Firstly, patients without del(17p)/*TP53* mutation were excluded, reducing the sample size of the population of interest to 25 for the VenG arm from the CLL14 trial and 34 for the ibrutinib arm from Ahn et al. Note that Ahn et al (2018), did not report on the required matching variables, including age, for the treatment-naïve del(17p)/*TP53* mutation population. Therefore, the 34 patients in the ibrutinib arm could have better prognostic features, such as being younger in age or having fewer comorbidities, factors which we couldn't account for in presented analyses but are expected to impact relative efficacy between arms.

Unadjusted HR of PFS

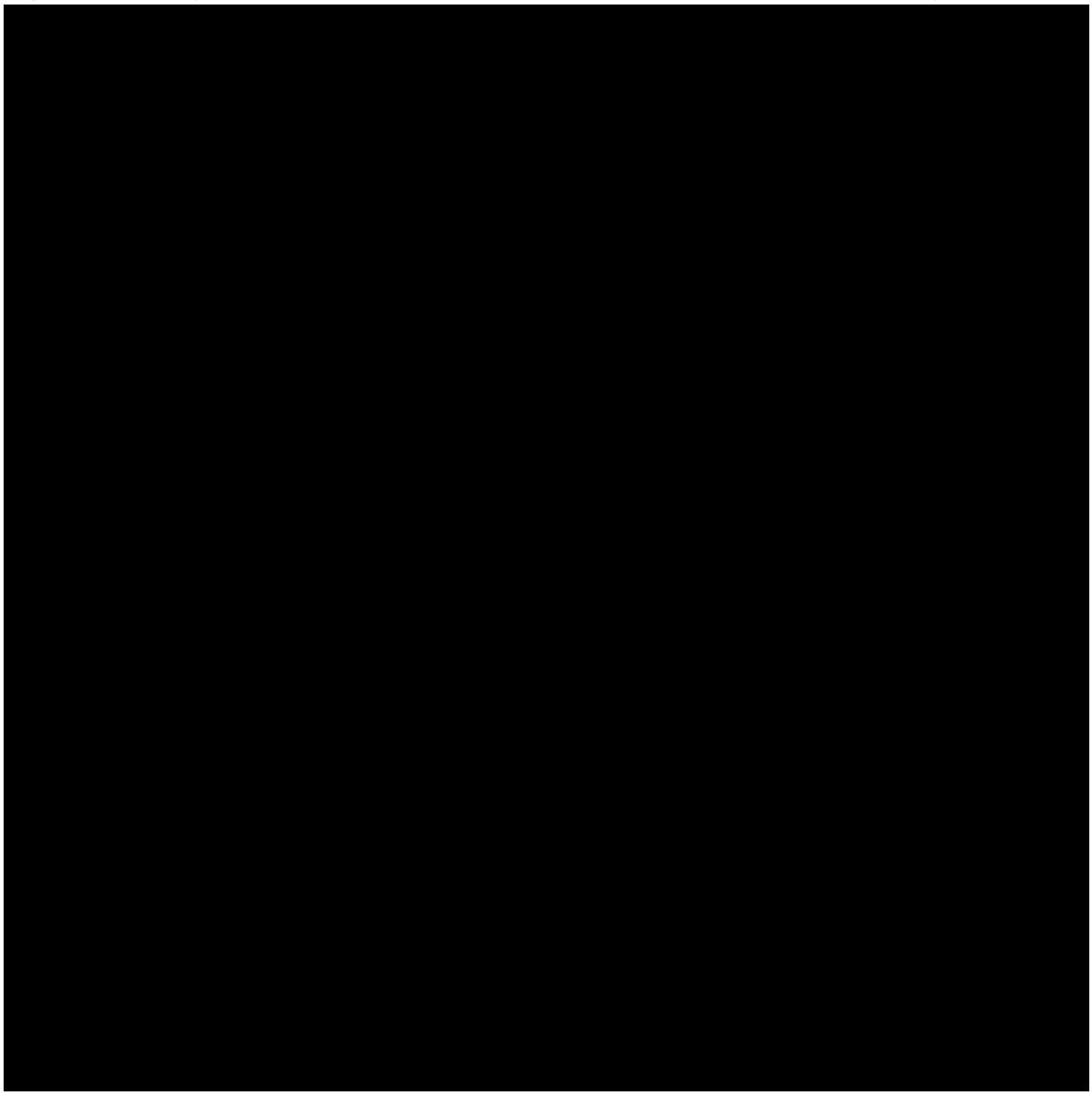
Table 10 and Figure 11 present the results for PFS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation. The naïve comparison estimates a HR of [redacted] (95% CI: [redacted]) ([redacted]). However, no conclusions can be drawn as patient numbers in each arm are low and important prognostic features, such as age and comorbidities, have not been adjusted for.

Table 10: Unadjusted HR of PFS between VenG and ibrutinib (Ahn et al. study)

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value
Ibrutinib (VenG reference)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 11: Unadjusted HR of PFS between VenG and ibrutinib (Ahn et al. study)



Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: Ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Unadjusted HR of OS

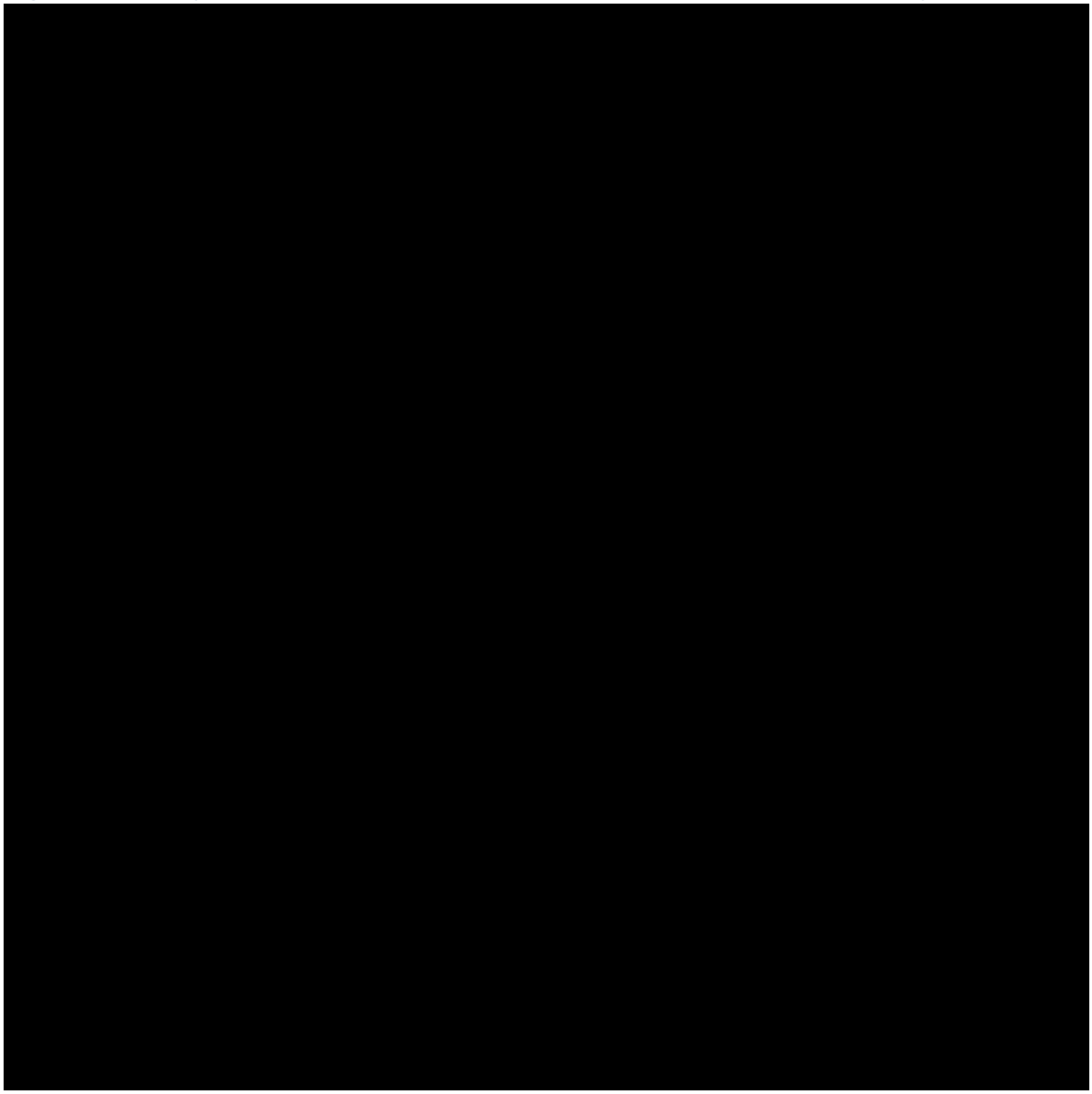
Table 9 and Figure 10 present the results for OS comparing ibrutinib versus VenG in previously untreated CLL patients unsuitable for fludarabine, cyclophosphamide and rituximab (FCR)/BR with del(17p)/*TP53* mutation. The naïve comparison estimates a HR of [redacted] (95% CI: [redacted]). However, the results are not statistically significant (log rank test: p = 0.132), with wide CIs.

Table 11: Unadjusted HR of OS between VenG and ibrutinib (Ahn et al. study)

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value
Ibrutinib VenG (reference)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; VenG: venetoclax with obinutuzumab.

Figure 12: Unadjusted HR of OS between VenG and ibrutinib (Ahn et al. study)



Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; OS: overall survival; VenG: venetoclax with obinutuzumab.

A.2.11 *Adverse events (AEs)*

As of the August 2019 clinical cut-off date, after an additional 12 months of follow-up, [redacted] additional fatal AEs were observed in both arms, while [redacted] additional and [redacted] additional drug-related serious AEs (SAEs) were observed in the GClb arm and VenG arms, respectively (Table 12).

Table 12: Overview of AEs (safety evaluable population)

	August 2018 data cut		August 2019 data cut	
Category, n (%)	**GClb (N=214)**	**VenG (N=212)**	**GClb (N=214)**	**VenG (N=212)**
Total number of patients with ≥1 AE	[redacted]	[redacted]	[redacted]	[redacted]
Total number of deaths (all deaths)*	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients with ≥1 event				
AE with fatal outcome	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
Related SAE	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3/4 AE (at greatest intensity)	[redacted]	[redacted]	[redacted]	[redacted]

Any minor changes in numbers are likely due to data cleaning or administrative updates.
*In the GClb arm, [redacted] in the ITT population died; therefore, the number of deaths in the safety population is [redacted] than in presentations of the ITT population. In the VenG arm, [redacted] is not represented in this display of events. Death was specified on the study completion/early discontinuation form; however, [redacted] is not included in other presentation of deaths. No further details of death are available for [redacted].
Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; SAE: serious adverse event; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A review of the updated AEs, regardless of severity or relationship to study drug, revealed [redacted] in the number of patients with most frequently reported AEs (neutropenia, infusion related reaction, thrombocytopenia, diarrhoea, nausea, pyrexia, anaemia, fatigue, cough, constipation, and headache), defined as events occurring in ≥10% of patients, in the VenG arm. There was [redacted] in the total number of TEAEs reported in the post-treatment period (≥29 days after last dose of venetoclax).

SAEs

The frequency of patients with SAEs was numerically [redacted] in the VenG arm ([redacted] patients[redacted]) compared with the GClb arm ([redacted] patients [redacted]).

Of the frequently reported events, [redacted] patients in the VenG arm had an SAE of [redacted]; these events occurred in the post-treatment period. Other minor changes in frequency of events (e.g. [redacted] patient with an event of [redacted] in the VenG arm) were noted in the current dataset, which are likely due to data cleaning activities.

The most common SAE in both treatment arms during the post-treatment period was [redacted] ([redacted] in the VenG arm; [redacted] in the GClb arm); [redacted] are new in the VenG arm and [redacted] are new in the GClb arm. [redacted] and [redacted] new events of [redacted] were also

reported since the primary clinical cut-off date in the VenG and GClb arms, respectively. All other new events since the primary clinical cut-off (August 2018) date were [redacted].

Table 13: Overview of SAEs reported in >1 patient in either treatment group during the post-treatment period (safety evaluable population)

	VenG (N=202)	GClb (N=208)
≥1 SAE during the post-treatment period – no. of patients (%)	[redacted][a]	[redacted][b]
SAEs reported in >1 patient in any treatment group during the post-treatment period – no. of patients (%)		
Infections and infestations		
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Blood and lymphatic system disorders		
Febrile neutropenia	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Prostate cancer	[redacted]	[redacted]
Nervous system disorders		
Cerebral ischaemia	[redacted]	[redacted]
Cardiac disorders		
Atrial fibrillation	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Metabolism and nutrition disorders		
Dehydration	[redacted]	[redacted]
Vascular disorders		
Hypertension	[redacted]	[redacted]
Ear and labyrinth disorders		
Vertigo	[redacted]	[redacted]

[a] In the VenG arm, incidence of events during the combination period and single agent treatment period was [redacted] and [redacted], respectively.
[b] In the GClb arm, incidence of events during the combination period and single agent treatment period was [redacted] and [redacted], respectively.
Abbreviations: GClb: chlorambucil with obinutuzumab; SAE: serious adverse event; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

Patient deaths

As of August 2019, in the ITT population, there were [redacted] deaths in the GClb arm ([redacted] died prior to receiving treatment) and [redacted] in the VenG arm; [redacted] additional deaths were reported in the VenG arm since the previous August 2018 data cut-off, and [redacted] for GClb The reasons for death are outlined in Table 14. Fatal AEs occurred in [redacted] patients ([redacted] in the VenG arm and [redacted]

patients ([redacted] in the GClb arm. Death due to PD occurred in [redacted] patients ([redacted]) in the VenG arm and [redacted] patients ([redacted]) in the GClb arm.

Table 14: Reasons for death (ITT population)

	Number of patients, n (%)	
	VenG (N=216)	GClb (N=216)
Death	[redacted]	[redacted]
AE	[redacted]	[redacted]
Acute myeloid leukaemia	[redacted]	[redacted]
Bladder cancer	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Cerebral ischaemia	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Encephalitis	[redacted]	[redacted]
Immune thrombocytopenic purpura	[redacted]	[redacted]
Metastatic malignant melanoma	[redacted]	[redacted]
Myelodysplastic syndrome	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
Pancreatic carcinoma metastatic	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pneumonia fungal	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Renal failure	[redacted]	[redacted]
Sarcoma of skin	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Skin squamous cell carcinoma metastatic	[redacted]	[redacted]
Squamous cell carcinoma of skin	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Other[e]	[redacted]	[redacted]
Infection[f]	[redacted]	[redacted]
Cardiogenic shock and septic[g]	[redacted]	[redacted]
Natural cardiac death	[redacted]	[redacted]
Patient died suddenly[h]	[redacted]	[redacted]
Respiratory sepsis[i]	[redacted]	[redacted]
Richter's transformation of CLL, unstable diabetes and DKA, multiple resistant infections, liver impairment[h]	[redacted]	[redacted]
Sepsis[h]	[redacted]	[redacted]
Unknown[h]	[redacted]	[redacted]

*Indicates death is new in the August 2019 data cut. These deaths each occurred >1 year following the last dose of study treatment. If there was another event reported in the same category in the primary CSR, additional details are provided in the footnotes below.

[a] [redacted] in the VenG arm is not represented in this display of events. Death was only specified on the study completion/early discontinuation form for [redacted]. No further details of death are available for [redacted].

[b] In the VenG arm, [redacted] of the fatal events of sepsis is new in the August 2019 data cut.

[c] In the GClb arm, [redacted] of the fatal events of septic shock is new in the August 2019 data cut.

[d] In the August 2019 data cut, [redacted] and [redacted] additional deaths due to disease progression were reported in the VenG and GClb arms, respectively. In the VenG arm, [redacted] of the deaths due to disease progression was reclassified by the investigator from a fatal event of infection during data verification.

[e] Patients in the 'Other' category had "death" specified as a reason for study discontinuation and the cause of death reported on the death case report form is shown in the table. [redacted] of these patients had fatal AEs. [redacted] deaths occurred ≥100 days after the last dose of study treatment. [redacted] in each treatment arm had discontinued study drug due to an AE prior to the event of death; details are provided in subsequent footnotes.

[redacted].

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

Source: AbbVie Data on File (CLL14 Clinical Study Report Supplement)[4] (August 2019 data cut: 39.6 months follow-up).

A.3 Cost effectiveness

This addendum to the already submitted economic evaluation of VenG in previously untreated CLL uses newer cut-off data from the main pivotal trial (CLL14; August 2019). This additional data was incorporated into the model version with the title "[B2] [B7] [B8] ID1402 (ACIC)_VenG_CLL_NICE Economic Model", which was previously shared with NICE in response to the Evidence Review Group's (ERG) clarification questions. The model updates, with reference to specific NICE submission sections, are explained in detail below.

1. Update of all survival analyses for modelled outcomes (PFS, OS, TTNT) using individual patient level data from the CLL14 August 2019 data cut. Changes were applied to both modelled populations (with del(17p)/*TP53* mutation or without).

2. Update of CLL14 patient allocation, and corresponding baseline information, to either of the two modelled populations (with del(17p)/*TP53* mutation or without).

3. Update of HRs as generated from the naïve comparison to ibrutinib data from relevant literature sources.[1, 2] Changes only apply to the del(17p)/*TP53* mutation population.

4. Update of the time-on-treatment information as per the August 2019 data cut. Changes were applied to both modelled populations (with del(17p)/*TP53* mutation or without).

5. Update of modelled serious treatment emergent AEs which had an incidence of ≥1% in the key trial arms for each included treatment. Changes were applied to both modelled populations (with del(17p)/*TP53* mutation or without).

A.3.1 *Overview of economic model results*

The same methodology as applied in the original submission is utilised here (refer to section B.3 of the original submission for details). Table 15 summarises the results of the updated economic model, based on analyses of the CLL14 August 2019 data cut.

Table 15 – Overview of updated economic model results

Section	Results
Survival analyses	• The survival models utilised in the original submission were utilised here, except for the TTNT extrapolation, which used an independent (log-logistic) model applied to CLL14 data for both the VenG and GClb arms (the original submission used an independent, Weibull model)
Base case analysis: non-del(17p)/*TP53* mutation population	• Similar to the original model results, VenG dominated GClb in the deterministic analysis • The key driver of relative cost-effectiveness was the difference in PFS, with a larger proportion of patients remaining progression free in the VenG arm compared with the GClb arm • The estimated duration of PFS is [redacted] years and [redacted] years for VenG and GClb, respectively • As a result, the costs of post-progression health state, driven by costly second line innovative therapies, were significantly higher in the GClb arm
Base case analysis: del(17p)/*TP53*	• Similar to the original model results, VenG was cost-effective versus ibrutinib in the deterministic analysis

mutation population	• The driver of the ICER values was ibrutinib costs resulting from the treat-to-progression regimen, with a mean treatment duration of 1358 days, compared to the fixed-treatment duration for VenG, of 316.14 days
Sensitivity analyses	Similar to the original model results: • Probabilistic ICERs were similar to deterministic ICERs (remaining dominant and cost-effective in the non-del(17p)/*TP53* and del(17p)/*TP53* populations respectively), whilst all scenarios tested found VenG to remain cost-effective (mostly dominant), save for unrealistically short model time horizons, demonstrating that ICERs were relatively stable to changes in the methods for survival analysis • As expected, deterministic sensitivity analyses on extreme parameter values found the model to be most sensitive to estimates of age and PPS and PFS utility values • The scenario analysis demonstrated that VenG is consistently cost-effective when compared to GClb or ibrutinib, with all but one scenario in each population resulting in a positive NMB at £30,000/QALY
Conclusions	Similar to the original model results: • Results of the base case analysis show that VenG is a cost-effective option at £30,000/QALY in the deterministic and probabilistic analyses • Probabilistic sensitivity analyses were consistent with the deterministic results, showing a [redacted] probability of being cost-effective in both the non-del(17p)/*TP53* and del(17p)/*TP53* mutation populations at the threshold of £30,000/QALY gained • Deterministic and probabilistic sensitivity analyses, and additional scenario analyses, demonstrated that the model results and conclusions were robust to input range and assumption changes

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

A.3.2 *Economic analysis*

A.3.2.1 Patient population (Section B.3.2.1)

The economic evaluation presented in this addendum aligns with the decision problem described in Table 2, Section B.1.1 of the main submission document, and utilises data from the Phase III randomised trial, CLL14 (August 2019 data cut: 39.6 months follow-up).

The analysis demonstrates the benefits of VenG compared with relevant treatments for two distinct patient groups:

- Patients without del(17p)/*TP53* mutation, compared with GClb (CLL14;[1] n=391)
- Patients with del(17p)/*TP53* mutation, compared with ibrutinib (CLL14 compared with Mato et al.;[2] n=31)

The algorithm used for assigning subpopulations was presented in the original submission (Section B.3.2.1), along with the reason for the difference between the CSR analysis and the cost-effectiveness model (CEM) analysis. Please also refer to AbbVie's response to the first set of ERG clarification questions. Patients with non-evaluable status (n=10) were excluded from the analyses (Table 16).

Table 16: Population numbers utilised in the CSR and CEM analyses (Table 32 of original submission)

	CSR analysis	CEM analysis
Non-del(17p)/*TP53* mutation	368	391
Del(17p)/*TP53* mutation	49	31
Undefined	15	10
Total	432	432

Abbreviations: CEM: cost-effectiveness model; CSR: clinical study report.

A.3.2.2 Model structure (Section B.3.2.2)

Please refer to section B.3.2.2 of the original submission for details of the model structure. The key features of the economic analysis are presented in Table 33 of the original submission and remain the same for the updated economic model except for the change outlined in Table 17 below. For the TTNT outcome, updated analyses rendered the independent model, log-logistic distribution as the most suitable base case selection taking into account the proportional hazards assumption, the best statistical fit and comparison to the new observed data.

Table 17: Changes to the key features of the economic analysis

Key feature	Chosen values in original submission	Chosen values in this addendum
TTNT extrapolation	Independent model, Weibull distribution	Independent model, log-logistic distribution

Abbreviations: TTNT: time-to-next treatment.

A.3.2.3 Intervention technology and comparators (Section B.3.2.3)

Please refer to section B.3.2.3 of the original submission for details of the intervention technology and comparators. The changes to the mean time-on-treatment (ToT) are presented in Table 18.

Table 18: Changes to mean time-on-treatment

	August 2018 data cut	August 2019 data cut
Venetoclax	313.6 days	316.14 days
Obinutuzumab	295.7 days	295.65 days

A.3.3 *Clinical parameters and variables*

A.3.3.1 Baseline characteristics (Section B.3.3.1)

Please refer to section B.3.3.1 (Table 34) of the original submission for details of the baseline characteristics. Updated baseline characteristics are presented in Table 19.

Table 19: CLL14 study data for the two modelled populations based on the August 2019 data cut (Table 34 of original submission)

	Application in the model	
Variable	**Non-del(17p)/*TP53***	**Del(17p)/*TP53***
Mean age, years	71.1	69.6
Male, %	66.4%	67.7%

Mean bodyweight, kg	75.6	78.2
Mean height, cm	168.8	167.9
Mean body surface area, m^{2*}	1.9	1.9
PFS (used for long-term extrapolations)	See Section A.3.3.4	
OS (used for long-term extrapolations)	See Section A.3.3.5	
TTNT (used for long-term extrapolations)	See Section A.3.3.6	
Mean ToT	VenG: 316.14 days GClb: 295.65 days	VenG: 295.31 days Ibrutinib: 1,358 days**
AE incidence (Serious TEAE with >1% incidence)	See Section A.3.3.10	
Treatment courses (used to calculate costs of first-line treatments)	Unchanged from original submission	
Utilities (explored in scenario analysis)	See Section A.3.8.3	

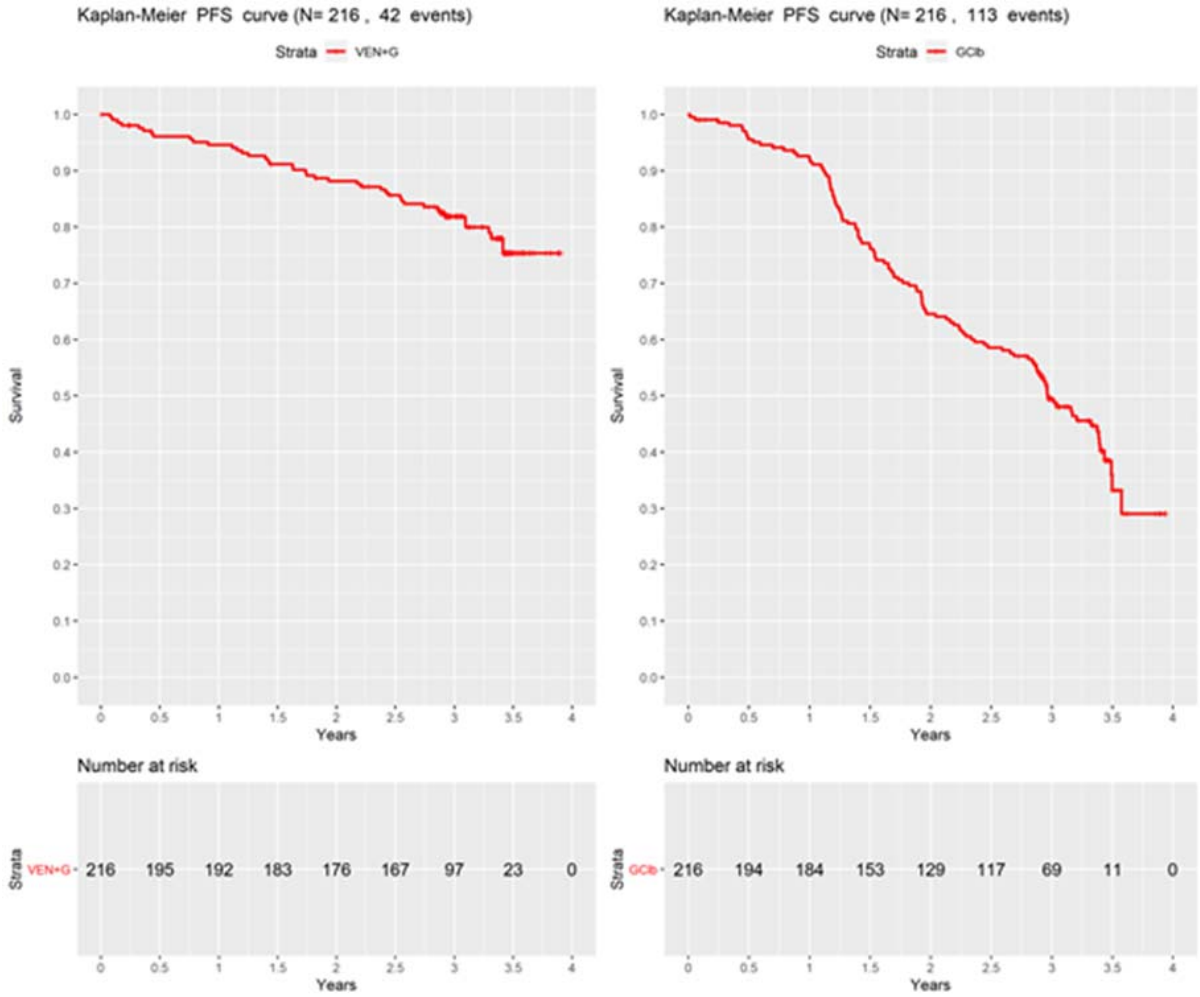
Calculated by the Dubois method: 0.007184(height^0.725)*(weight^0.425)
**The mean ToT for ibrutinib is sourced from the base case PFS analysis using the HR from Mato et al.[2] and remains unchanged as per the original submission.
Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; TEAE: treatment-emergent adverse event; ToT: time-on-treatment; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

A.3.3.2 Overview of time-to-event data (Section B.3.3.2)

Figure 13, Figure 14, Figure 15, and Figure 16 present the Kaplan–Meier curves and numbers at risk for PFS, OS, TTNT and ToT, respectively, for both VenG and GClb over the observed time period in CLL14.

Figure 13 presents PFS data from CLL14 investigator-assessed analyses (endpoint used in the economic model). The primary efficacy analysis demonstrated a significant PFS benefit (HR 0.31; 95% CI: 0.22, 0.44; p<0.01) for patients in the VenG arm ([redacted] events) compared with patients in the GClb arm ([redacted] events). Median PFS in the VenG arm was not reached and median PFS in the GClb arm was 35.6 months (95% CI: [redacted]). The difference in PFS at 3 years (36 months) post-randomisation is apparent, with PFS in the VenG arm as high as 81.9%, compared to 49.5% for the GClb arm. It is important to note the clear separation between arms, especially after the first 12 months of treatment, which drives the extrapolated model outcomes.

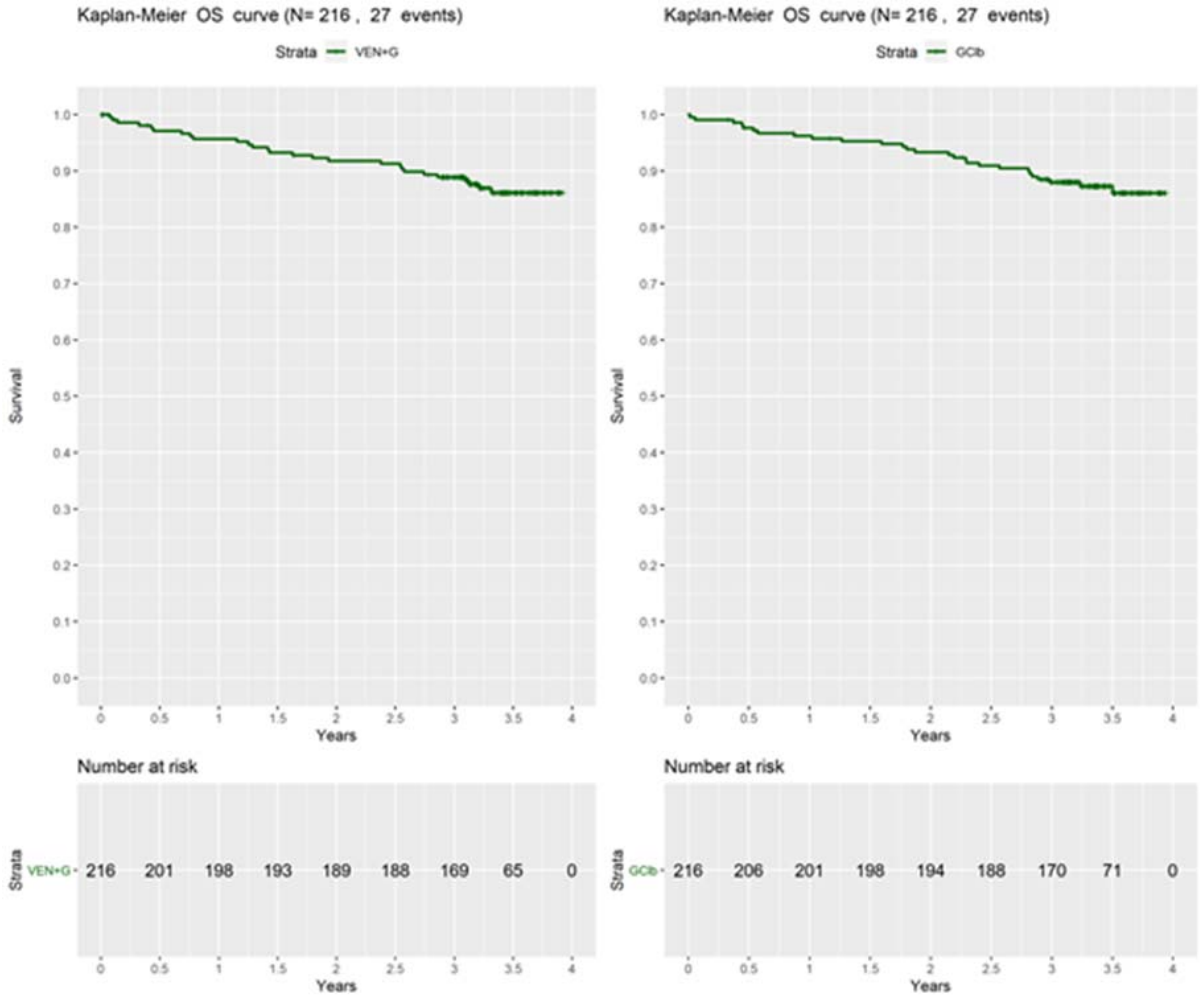
Figure 13: Kaplan–Meier plots for investigator-assessed PFS



Abbreviations: GCIb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 14 presents OS data from the CLL14 trial. Overall, a total of [redacted] randomised patients in the intention-to-treat (ITT) population had died; [redacted] patients ([redacted]) in each treatment arm. The OS data remain too immature, for a first-line CLL population, to be meaningful thus the median OS was not reached in either arm. In summary, there is no evidence of difference in OS between arms and this is aligned with base case selection submitted as part of the original submission (OS assumed equal between arms for the modelled population without del(17p) mutation). The observed trend is explained by confounding factors, such as previous medical history, concurrent illnesses and latency of AE onset following last treatment dose. Death due to PD occurred in [redacted] ([redacted]) patients in the VenG arm and [redacted] ([redacted]) patients in the GCIb arm, highlighting the value of venetoclax in reducing the chance of dying due to CLL PD.

Figure 14: Kaplan–Meier plots for OS



Abbreviations: GCIb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

In Figure 15, Kaplan–Meier data for TTNT are presented, with [redacted] fewer patients moving to next treatment for the VenG arm ([redacted] events) compared to GCIb ([redacted] events). This trend demonstrates that VenG delays and reduces the need for subsequent treatment.

Figure 15: Kaplan–Meier plots for TTNT

Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

Figure 16 presents Kaplan–Meier plots for average ToT in each CLL14 treatment arm. Median duration of exposure to venetoclax, from the first venetoclax dose, was [redacted] days and the mean duration was [redacted] days.

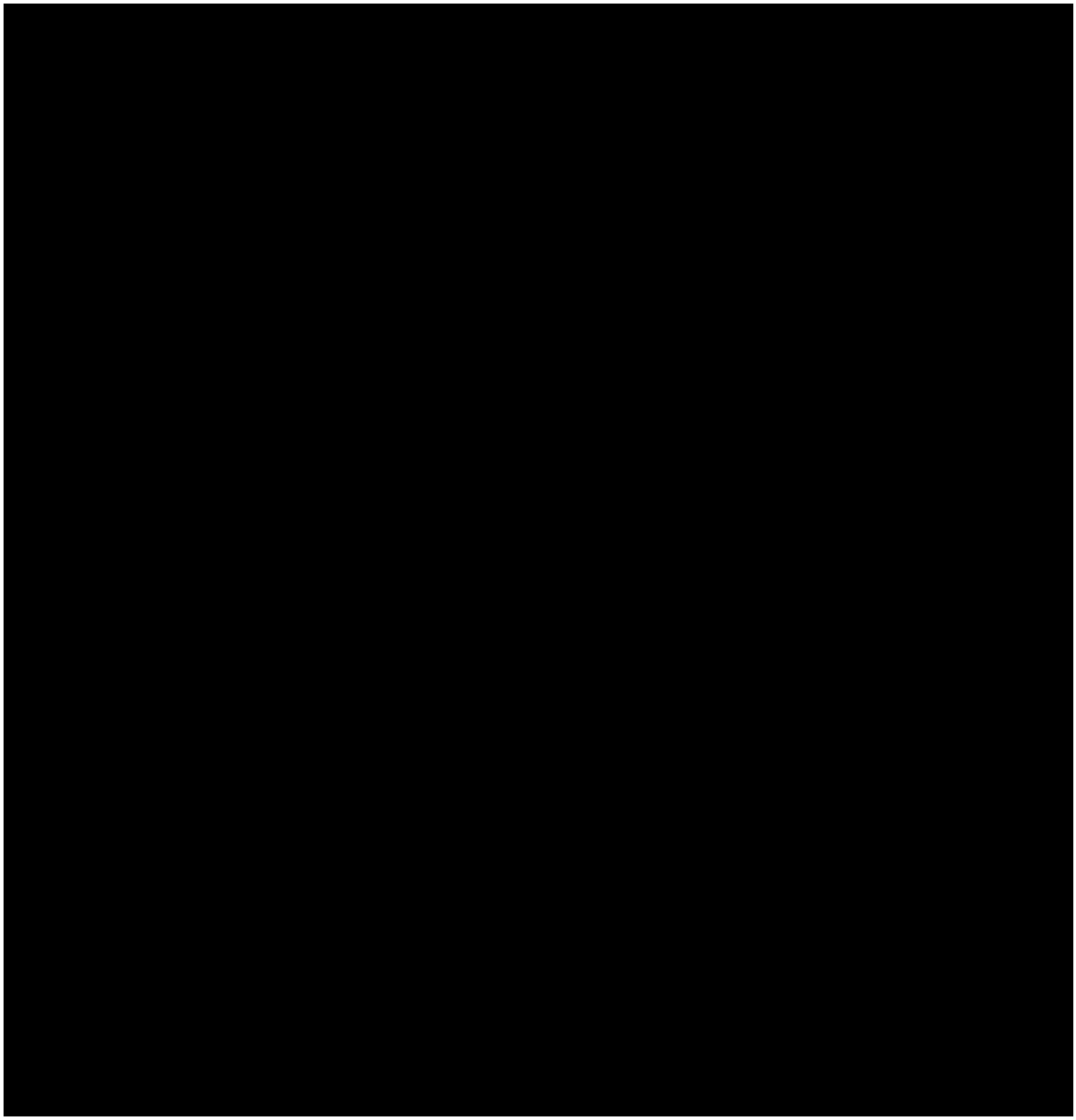
Figure 16: Kaplan–Meier plots for ToT

Abbreviations: GClb: chlorambucil with obinutuzumab; ToT: time-on-treatment; VenG: venetoclax with obinutuzumab.

A.3.3.3 Assessing the proportional hazards assumption

The conclusions on proportionality of hazards remain the same (please refer to Section B.3.3.3 of the original submission document). Graphs of this section were updated using the August 2019 data cut and are presented below.

Figure 17: Kaplan–Meier plots for OS and PFS and assessment of proportional hazards assumption between treatment arms

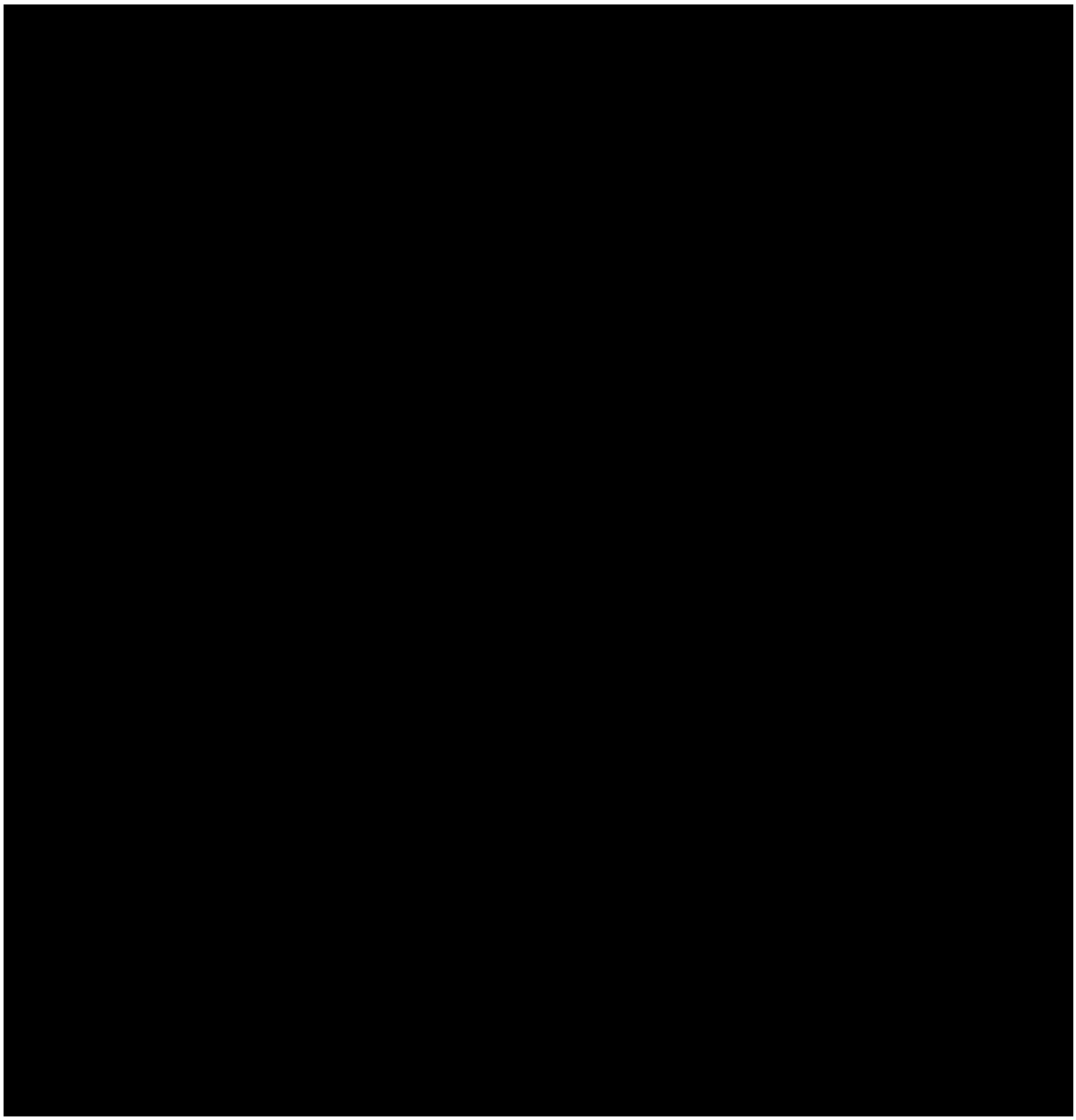


Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 18: Log cumulative hazard plots for PFS for VenG and GClb

Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 19: Kaplan–Meier plots for OS and PFS stratified by treatment arm and del(17p)/*TP53* mutation status, and assessment of proportional hazards assumption for OS and PFS

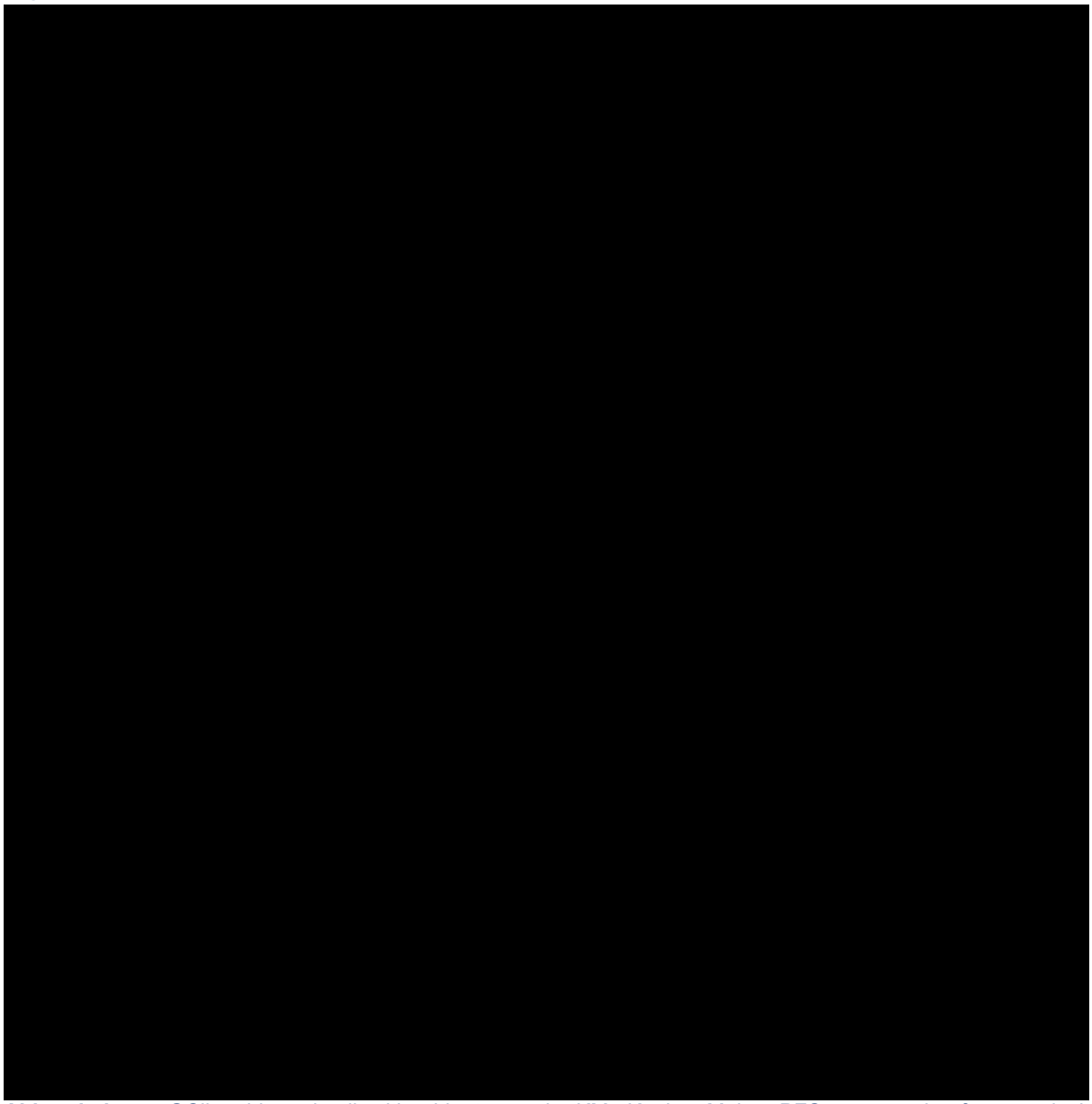


Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

A.3.3.4 PFS

Independent model (log-logistic) remains the base case selection for PFS. Summary statistics, long term extrapolations graph, and landmarks of this section were updated using the August 2019 data cut.

Figure 20: Parametric extrapolations for PFS for VenG and GClb (independent model)



Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Table 20: Model fit statistics (AIC and BIC) for the individual model extrapolations for PFS (independent model)

Distribution	AIC		BIC	
	VenG	GClb	VenG	GClb
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.

Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Table 21 presents the 5-, 10-, 20-, and 30-year landmark survival estimates from the individual modelling of PFS. Due to immature data for VenG and GClb, there was a large degree of variability in the predicted PFS over 20 years. While the Gompertz distribution provided the most appropriate statistical model fit for VenG, this was inappropriate to be used as the base case due to unrealistic long-term projections that underestimate PFS benefit in both arms.

Table 21 shows that, for the GClb arm, the log-logistic (at 5 years), and Weibull (at 5 years) distributions most closely align with long-term follow-up data from the CLL11 trial (of patients treated with GClb alive in PFS at five years). The independent (Log-logistic) was selected as the base case taking into account proportional hazards assumption, best statistical fit, and comparison to observed data from CLL11.

Table 21: Landmark survival for the individual model for PFS (independent model)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential								
Weibull								
Gompertz								
Log-logistic								
Log-normal								
Generalised gamma								

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

A.3.3.5 OS (all-cause death)

Dependent model (exponential) remains the base case selection for OS; Please refer to section B.3.3.6 of the original submission for base case selection rationale as this also applies to newer cut-off. Summary statistics, long term extrapolations graph and landmarks of this section were updated using the August 2019 data cut.

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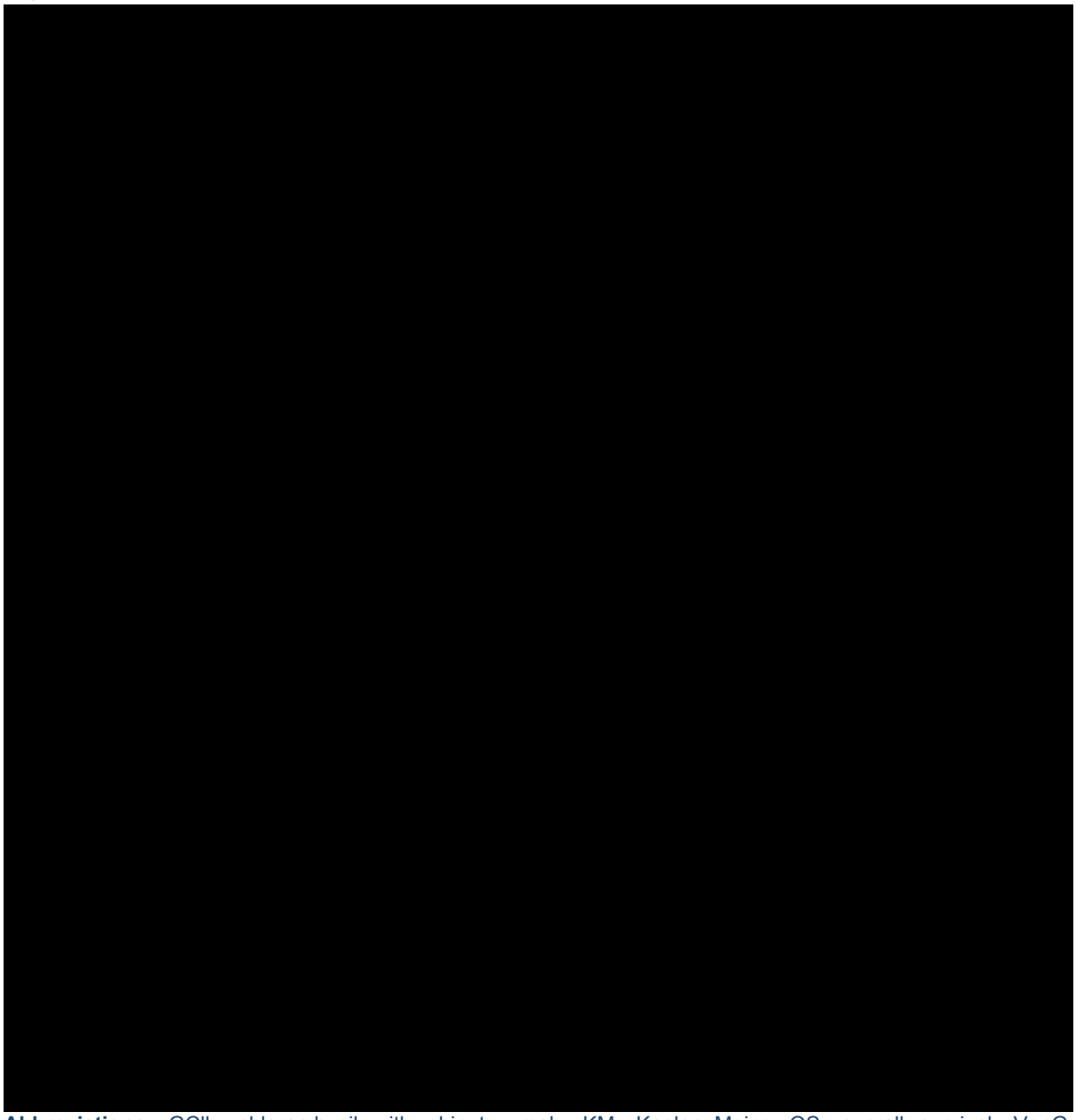
Figure 21: Parametric extrapolations for OS for VenG and GClb (dependent model)



Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; OS: overall survival; VenG: venetoclax with obinutuzumab.

Table 22: Model fit statistics (AIC and BIC) for the individual model extrapolations for OS (dependent model)

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

Notes: Bold indicates the base case.
Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; OS: overall survival.

Table 23: Landmark survival for the dependent model for OS (without treatment effect)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

CLL14 remains the most appropriate data source for the comparison of VenG to GClb. Nonetheless, a variety of approaches for modelling OS were explored for completeness due to CLL14 OS data immaturity. Please refer to section B.3.3.6 of the original submission for conclusions on the use of CLL11, RESONATE and Warwick network meta-analysis (NMA) as external sources of post-progression survival (PPS) in order to calculate OS benefit outside of what is seen in CLL14. Corresponding figures have been updated and are shown below.

The source of evidence providing the most plausible OS estimates was the CLL14 trial. Based on clinical expert opinion, and in the absence of statistically significant OS data from the CLL14 trial, the treatment effect of VenG and GClb was assumed to be the same. Of note, at approximately 3 years follow-up (August 2019 data cut), median OS has not been reached in either arm ([redacted] of patients in each treatment arm have died, HR 1.03; 95% CI: 0.60, 1.75; p=0.92).[4]

As discussed in section B.3.3.6 of the original submission, assuming VenG and GClb have a similar treatment effect is a conservative approach. There is published evidence of a positive correlation between uMRD and prolonged OS.[8]

Figure 22: Overall survival using CLL11 PPS data

The blue line for VenG is not visible as the same OS curve is applied to both trial arms of CLL14 (VenG and GClb [red]).
Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; PPS: post-progression survival; Ven+G: venetoclax with obinutuzumab.

Figure 23: Overall survival using RESONATE trial ibrutinib arm

The blue line for VenG is not visible as the same OS curve is applied to both trial arms of CLL14 (VenG and GClb [red]).
Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; Ven+G: venetoclax with obinutuzumab.

Figure 24: Overall survival using Warwick ERG NMA from NICE appraisal TA561

In this scenario, the OS projection curves are higher than general population mortality, and so background mortality is modelled instead.
Abbreviations: ERG: Evidence Review Group; GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; NMA: network meta-analysis; Ven+G: venetoclax with obinutuzumab.

Table 24 provides an overview of the resulting PPS life-years (LY) generated in the first-line CLL model as part of the validation exercise when using external data sources.

Table 24: PPS (LYs) following application of external data

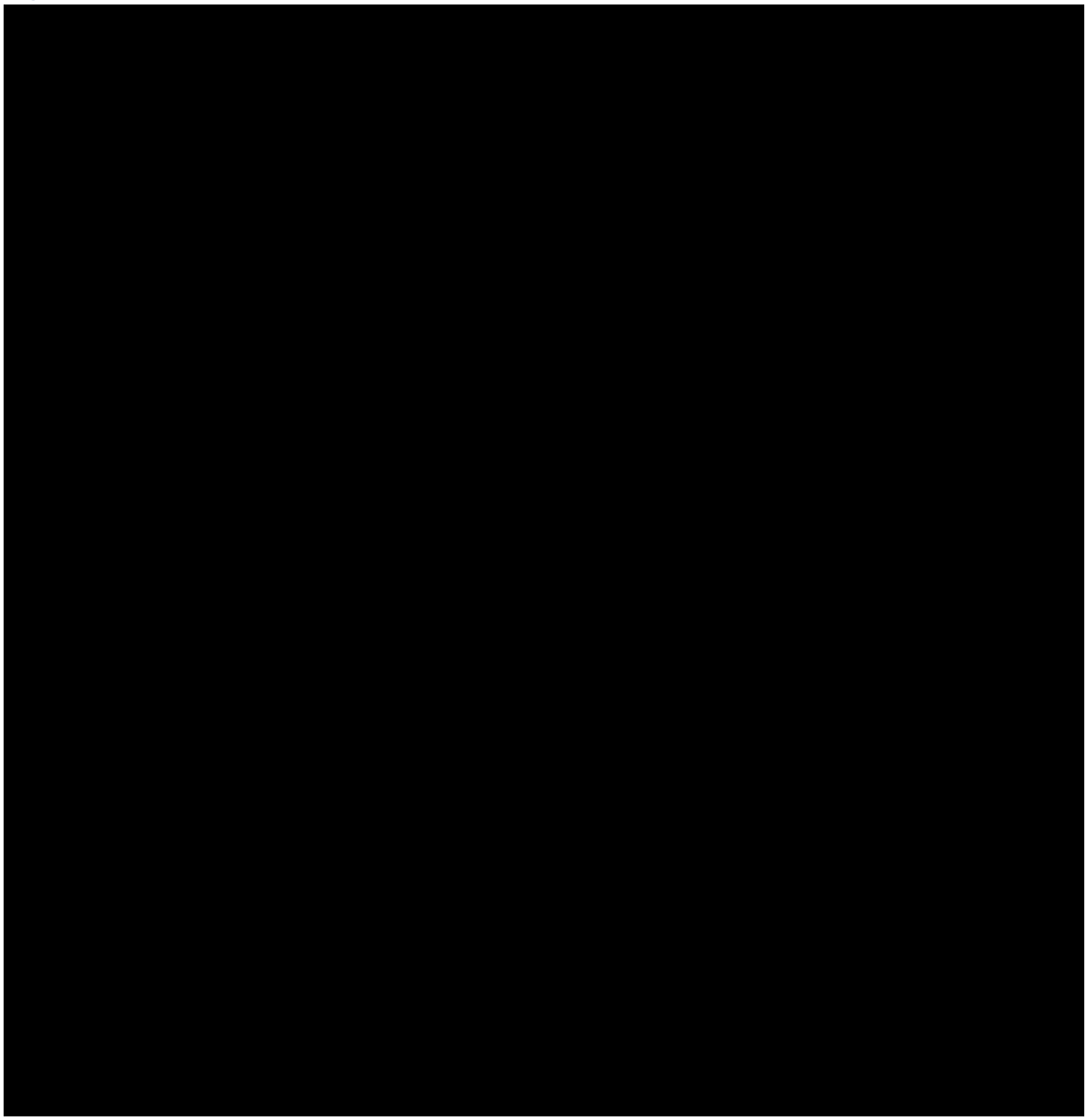
	PPS after application of external data, LYs	CLL14 PPS, LYs
CLL11 (GClb arm)	4.85	9.82
RESONATE (ibrutinib arm)	7.92	
Warwick ERG NMA, TA561 (ibrutinib arm)	10.33	

Abbreviations: ERG: Evidence Review Group; GClb: chlorambucil with obinutuzumab; LYs: life-years; NMA: network meta-analysis; PPS: post-progression survival.

A.3.3.6 TTNT

Independent model (log-logistic) is now the base case selection for TTNT. Summary statistics, long term extrapolations graph and landmarks of this section were updated using the August 2019 data cut.

Figure 25: Parametric extrapolations for TTNT for VenG and GClb (individual model)



Abbreviations: GClb: chlorambucil with obinutuzumab; KM: Kaplan–Meier; PFS: progression-free survival; TTNT: time-to-next- treatment; VenG: venetoclax with obinutuzumab.

Table 25: Model fit statistics (AIC and BIC) for the individual model extrapolations for TTNT (independent model)

	AIC		BIC	
	VenG	GClb	VenG	GClb
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: AIC: Akaike information criteria; BIC: Bayesian information criteria; GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

Survival analysis from the CLL11 trial reports that, at 5 years, [redacted] (95% CI: [redacted]) of patients had not experienced a next treatment event.[9] Aligned with the original submission, both the Weibull and log-logistic distributions are candidates for the base case and relatively close to the observed data from CLL11, please refer to section B.3.3.8 for more detail. Since with the August 2019 cut-off the log-logistic landmarks for GClb are now closer to observed data from CLL11 at 5-years (59.71% vs 49%), this was selected as the new base case to also align with PFS base case selection (log-logistic), an outcome highly correlated to TTNT. Moreover, the decreasing hazards over time associated with a log-logistic distribution align with the clinical expectation that the longer a patient remains in remission the less likely this patient is to require the next line of therapy.

Table 26: Landmark survival for the individual model for TTNT (independent model)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

A.3.3.7 ToT

As per the newer CLL14 cut-off (August 2019), the median ToT before discontinuation was achieved at [redacted] (mean [redacted]) for VenG versus [redacted] (mean [redacted]) for GClb. Updated Kaplan–Meier data are presented in Figure 26.

Figure 26: Kaplan–Meier plots for ToT for VenG and GClb

Abbreviations: GClb: chlorambucil with obinutuzumab; ToT: time on treatment; VenG: venetoclax with obinutuzumab.

A.3.3.8 PFS and OS for ibrutinib in the del(17p)/*TP53* population

In the CLL14 trial, there were 25 patients in the VenG arm with del(17p)/*TP53* mutation status. Kaplan–Meier plots from this subgroup were naïvely compared to those provided by the ibrutinib source for the same timeframe, or longer. This was done to ensure consistency between information from CLL14 and published literature (i.e. patients with *TP53* aberrations). Information from the curves on the numbers of patients at risk were used to calculate a HR comparing patients with del(17p)/*TP53* mutation on VenG in the CLL14 trial with patients with del(17p)/*TP53* mutation in the ibrutinib studies.

The PFS HR from the naïve comparison was combined with the VenG PFS curve (Figure 27) for those patients with the del(17p)/*TP53* mutation to generate the individual ibrutinib PFS curve. Similarly, the OS HR from the naïve comparison was combined with the VenG OS curve (Figure 27) to generate the individual OS curve for those patients with a del(17p)/*TP53* mutation.

Figure 27 Kaplan–Meier plots for PFS and OS from CLL14 for VenG arm

Abbreviations: OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Table 27 shows the results of the naïve comparisons using both sources of evidence, with the extrapolated PFS and OS curves utilised in the model shown in Figure 28 and Figure 29, respectively. Caution should be applied when interpreting these figures since the data used in the analyses were retrieved from single arm studies. In addition, the naïve comparison method was selected since adjustment for prognostic factors was not feasible due to the limited information on patient characteristics available in the publications. Results from these analyses are driven by small sample sizes, creating a high level of uncertainty in the estimation of benefit differences between VenG and ibrutinib, as reflected by the broad CIs and lack of statistical significance.

Table 27: HRs for PFS and OS for the del(17p)/*TP53* mutation population using naïve comparisons

Ibrutinib versus VenG	PFS		OS	
	Mato et al.[2]	Ahn et al.[1]	Mato et al.[2]	Ahn et al.[1]
Mean HR	0.660	0.318	0.841	0.401
Standard error of ln(HR)	0.457	0.533	0.525	0.606
Lower 95% CI	0.270	0.112	0.301	0.123
Upper 95% CI	1.615	0.903	2.352	1.315

P-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 28: PFS curves utilised in model for VenG and ibrutinib for del(17p)/*TP53* mutation population

Abbreviations: Ibr: ibrutinib; KM: Kaplan-Meier; PFS: progression-free survival; Ven+G: venetoclax with obinutuzumab.

Figure 29: OS curves utilised in model for VenG and ibrutinib for del(17p)/*TP53* mutation population

Abbreviations: Ibr: ibrutinib; KM: Kaplan-Meier; OS: overall survival; Ven+G: venetoclax with obinutuzumab.

A.3.3.9 Base case survival extrapolations summary

PFS (versus GClb in non-del(17p)/*TP53*): As concluded in Section B.3.3.5 of the main submission, the log-logistic model was found to provide the most plausible long-term PFS estimates for GClb based on goodness of fit assessment, validation with external sources and UK clinical expert advice. Thus, the log-logistic model was applied to VenG and GClb in the base case.

PFS (versus ibrutinib in del(17p)/*TP53*): The naïve comparison to Mato et al.[2] estimated an HR of 0.660 (95% CI: 0.270, 1.615; p=0.3630), however it is not statistically significant with wide CIs, which is reflective of the very small sample sizes of the available data. Thus, no conclusions can be made about the relative PFS of ibrutinib versus VenG. It should also be noted that it was not feasible to adjust for between trial differences and this renders point estimates to further uncertainty. This HR was used in the base case extrapolations.

OS (versus GCIb in non-del(17p)/*TP53*): OS data in CLL14 are immature, driven by only a few events and are not statistically significant. The exponential distribution was selected for both arms in the base case as it provided the best visual fit when compared to the CLL14 observed data.

OS (versus ibrutinib in del(17p)/*TP53*): The naïve comparison to Mato et al.[2] estimated an HR of 0.841 (95% CI: 0.301, 2.352; p=0.741).[2] Similar to the PFS results, the OS results were not statistically significant and have wide CIs, which is reflective of the very small sample sizes of the available data. Thus, no conclusions could be made about the relative OS of ibrutinib versus VenG. This HR was used in the base case extrapolations. Additional scenario analyses were performed using a different data source from the literature (Ahn et al.[1]), but the small sample size also meant that no conclusions could be drawn. Finally, in line with the approach taken in the venetoclax with rituximab NICE appraisal, a scenario assuming equal efficacy between VenG and ibrutinib was also explored as an aid to decision making.[10]

TTNT: The log-logistic model was selected as the base case for both (VenG and GCIb) arms as it was considered the best statistical fit and the GCIb extrapolations generally aligned with observed data from CLL11.

External validation (CLL11 GCIb arm versus CLL14 GCIb arm): All extrapolations were externally validated using the CLL11 trial, and differences in landmark results (**Error! Not a valid bookmark self-reference.**) between the CLL11 GCIb arm and the CLL14 GCIb arm may be partly explained by innovation in treatments for relapsed/refractory CLL following the CLL11 trial.

Table 28: Five-year landmark survival comparison between CLL11 and CLL14

	GCIb CLL11 Kaplan–Meier data	GCIb CLL14 Extrapolation	Model used for extrapolation for CLL14
PFS: 5-year	24.35%	[redacted]	Log-logistic, independent model
OS: 5-year	66.7%	[redacted]	Exponential, dependent model
TTNT: 5-year	49.65%	[redacted]	Log-logistic, independent model

Abbreviations: GCIb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

Table 29 provides an overview of the base case distribution choices for each outcome, per treatment arm and population.

Table 29: Overview of base case distribution choices

Endpoint	Non-del(17p)/*TP53*	Del(17p)/*TP53*
PFS	VenG: Independent model, log-logistic GCIb: Independent model, log-logistic	VenG: Independent model, log-logistic Ibrutinib: Mato HR
OS	Dependent model, exponential distribution No treatment effect assumed	VenG: Dependent model, exponential distribution Ibrutinib: Mato HR

TTNT	VenG: Independent model, **log-logistic** GClb: Independent model, **log-logistic**	VenG: Independent model, **log-logistic** Ibrutinib: Incident patients who have progressed and not died
ToT	Non-del(17p) ToT curves per treatment arm from CLL14 trial	VenG: Del(17p)/*TP53* ToT curve for VenG from CLL14 trial Ibrutinib: PFS curve for ibrutinib

Bold indicates changes since the original submission.
Abbreviations: GClb: chlorambucil with obinutuzumab; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; ToT: time-on-treatment; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

A.3.3.10 AE probabilities

Table 30 provides the overview of the updated AE probabilities using the August 2019 CLL14 cut-off.

Table 30: Probabilities for serious treatment emergent AEs utilised in cost-effectiveness model (Grade 3, 4 or 5)

AE Incidence	VenG	GClb
Asthenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Source	CLL14[3]	CLL14[3]
Sample size	212	214

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

A.3.4 *Measurement and valuation of health effects*

A.3.4.1 Health-related quality-of-life (HRQoL) data used in the cost-effectiveness analysis

The previous NICE appraisal TA343 (GClb for untreated CLL) was used to inform the base case of the model, the results of which are presented in Table 31.[11]

Table 31: Base case utilities utilised in the model

Progression stage	Utility value	Source	Rationale for change/use
Pre-progression IV	0.670	TA343: PFS under IV treatment	VenG and GClb include IV treatment. This is applied for the fixed treatment duration of 12 months in the PFS state.
Pre-progression	0.820	TA343 Progression-free	VenG and GClb should not be taking into

off treatment		survival after initial treatment is completed (0.82)	account IV disutility for the complete time on PFS health state. A value higher than that of pre-progression oral treatment (0.71) treatment but lower than that of perfect health is a more suitable option.
Pre-progression oral treatment	0.710	TA343 for Progression-free survival under oral treatment	A utility value reflective of oral treatment should be applied for the Ibrutinib arm PFS state.
Post-progression	0.600	TA343*: weighted average of the following utilities (progression after first-line treatment, PFS ± second-line treatment, relapsed line of treatment)	Used as base case and aligned with what has been accepted in previous NICE CLL appraisals.[11, 12]

*Utility for the population considered (patients unsuitable for FCR/BR) is calculated as a weighted average of patients suitable and unsuitable for FCR/BR
Abbreviations: BR: bendamustine with rituximab; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

A.3.5 *Cost and healthcare resource use identification*

A.3.5.1 Treatment-specific monitoring costs: tumour lysis syndrome (TLS)

TLS rates and costs were updated using Fischer et al. (2019) and the August 2019 cut-off data.[5]

Table 32: TLS risk distribution for VenG and GClb treatment arms

Treatment	Lower risk (node diameter ≤5 cm and ALC <25 x 10^9)	Greater risk (node diameter >5 cm or ALC >25 x 10^9)	
		Creatinine clearance > 80 mL/min	Creatinine clearance ≤ 80 mL/min
VenG	[redacted]	[redacted]	[redacted]
GClb	[redacted]	[redacted]	[redacted]

Abbreviations: ALC: absolute lymphocyte count; GClb: chlorambucil with obinutuzumab; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.

Table 33 provides the cost split by risk of tumour burden and treatment arm. Please note the costs for the greater risk tumour burden patients are different across the VenG and GClb arms because the proportion of patients who receive rasburicase (an anti-hyperuricaemic agent used to prevent TLS) at baseline is different across these treatment arms.

Table 33: TLS cost split by tumour burden for VenG and GClb treatment arms

Treatment	Low tumour burden	Greater Risk (CrCl >80)	Greater Risk (CrCl ≤80)	Total cost used in model
VenG	£1411	£1,708	£2,230	£1,784
GClb	£1411	£1,489	£2,242	£1,629

Abbreviations: CrCl: creatinine clearance; GClb: chlorambucil with obinutuzumab; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.

Based on the TLS risk distribution and the prophylaxis algorithm, the cost of TLS prophylaxis applied to the VenG arm in the first cycle is £1,784, and £1,629 in the GClb arm.

A.3.6 *Summary of base case analysis inputs*

Please refer to section B.3.6.1 (Table 63) of the original submission for a summary of the base case analysis inputs. The main change based on the updated August 2019 data cut is described in Table 34.

Table 34: Changes to base case analysis inputs based on the August 2019 data cut

Variable	Original submission	Addendum
Non-del(17p)/*TP53*		
Source of effectiveness: TTNT	• **VenG:** Independent model, Weibull • **GClb:** Independent model, Weibull	• **VenG:** Independent model, log-logistic • **GClb:** Independent model, log-logistic

Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

A.3.6.1 Assumptions

Please refer to section B.3.6.2 (Table 64) of the original submission for a summary of the model assumptions. The main change based on the updated August 2019 data cut is described in Table 35.

Table 35: Changes to assumptions based on the August 2019 data cut

Variable	Original submission	Addendum	Rationale
TTNT	A Weibull distribution was chosen, based on statistical fit and validation of the GClb treatment arm (using CLL14 trial data that were validated with published CLL11 data for GClb arm)	A log-logistic distribution was chosen, based on statistical fit and validation of the GClb treatment arm (using CLL14 trial data that were validated with published CLL11 data for GClb arm)	Almost identical fit between Weibull and log-logistic distributions and similar AIC/BIC values. Log-logistic was selected to align with PFS base case selection and clinical expectation on likelihood of requiring subsequent treatments in the long-run (as per the hazard function).

Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment.

A.3.7 *Base case results*

Base case results for the cost-effectiveness analysis are presented in the following subsections, for both the del(17p)/*TP53* and non-del(17p)/*TP53* populations. Base case results are presented as follows:

- List price of VenG versus list price of all comparators (GClb and ibrutinib)
- PAS price of venetoclax only (obinutuzumab remains at list price) versus list price of all comparators (GClb and ibrutinib)

The ERG will undertake similar comparisons using the confidential discounted prices for obinutuzumab and ibrutinib and share these with the appraisal committee.

A.3.7.1 Base case incremental cost-effectiveness analysis results

The base case deterministic cost-effectiveness results are provided for list price and with venetoclax PAS price in Table 36 and Table 37, respectively. In the non-del(17p)/*TP53* mutation population VenG was associated with higher average quality-adjusted life years (QALYs) and lower average costs versus GClb meaning that VenG is dominant versus GClb in this population. In the del(17p)/*TP53* mutation population VenG generated lower average QALYs and costs versus ibrutinib, but still resulted in a positive net monetary benefit (NMB) at a £30,000/QALY threshold.

In the non-del(17p)/*TP53* mutation population, cost-effectiveness is largely driven by an increase in progression-free LYs, and a reduction in subsequent costs following progression compared to GClb. In the del(17p)/*TP53* mutation population, the driver of the ICER values is the medication costs of ibrutinib (treatment continues until patients progress; mean of 1,358 days) versus fixed treatment duration for VenG (mean of 316.14 days; see company submission Section B.3.3.1 and Section B.3.3.8).

Table 36: Base case results at VenG list price (deterministic)

Treatment	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	14.141	6.742				
VenG	[redacted]	14.141	7.799	[redacted]	0.000	1.057	Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	7.536	4.153				
VenG	[redacted]	6.467	3.991	[redacted]	−1.069	−0.163	[redacted]

*This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold. Positive NMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NMB: net monetary benefit; VenG: venetoclax with obinutuzumab.

Table 37: Base case results at venetoclax PAS price* (deterministic)

Treatment	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	14.141	6.742				
VenG	[redacted]	14.141	7.799	−£136,550	0.000	1.057	Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	7.536	4.153				
VenG	[redacted]	6.467	3.991	−£280,896	−1.069	−0.163	£1,727,509**

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
**This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold. Positive NMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NMB: net monetary benefit; VenG: venetoclax with obinutuzumab.

A.3.8 *Sensitivity analyses*

A.3.8.1 Probabilistic sensitivity analysis (PSA)

PSA were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 simulations, in order to calculate the uncertainty in costs and outcomes. In cases where uncertainty data were not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The base case probabilistic results for list price and with venetoclax PAS price are provided in Table 38 and Table 39, respectively. The probabilistic results are broadly in line with the deterministic results, showing that the model is relatively stable when tested for uncertainty and that VenG is dominant versus GClb and a cost-effective treatment option versus ibrutinib.

Table 38: Base case results at VenG list price (probabilistic)

Treatment	Total costs, £ (95% CI)	Total LYG	Total QALYs (95% CI)	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	NR	6.673 (5.617, 7.597)		NR		
VenG	[redacted]	NR	7.699 (6.259, 8.866)	−[redacted]	NR	1.027	Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	NR	4.089 (1.497, 6.978)		NR		
VenG	[redacted]	NR	3.94 (2.302, 5.67)	−[redacted]	NR	−0.149	[redacted]*

*This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold.
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LYG: life years gained.

Table 39: Base case results at venetoclax PAS price* (probabilistic)

Treatment	Total costs, £ (95% CI)	Total LYG	Total QALYs (95% CI)	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	NR	6.654 (5.596, 7.635)		NR		
VenG	[redacted]	NR	7.696 (6.156, 8.819)	−£127,293	NR	1.042	Dominant
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	NR	4.071 (1.547, 7.015)		NR		
VenG	[redacted]	NR	3.947 (2.375, 5.671)	−£205,595	NR	−0.124	£1,654,610.12**

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
**This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold.

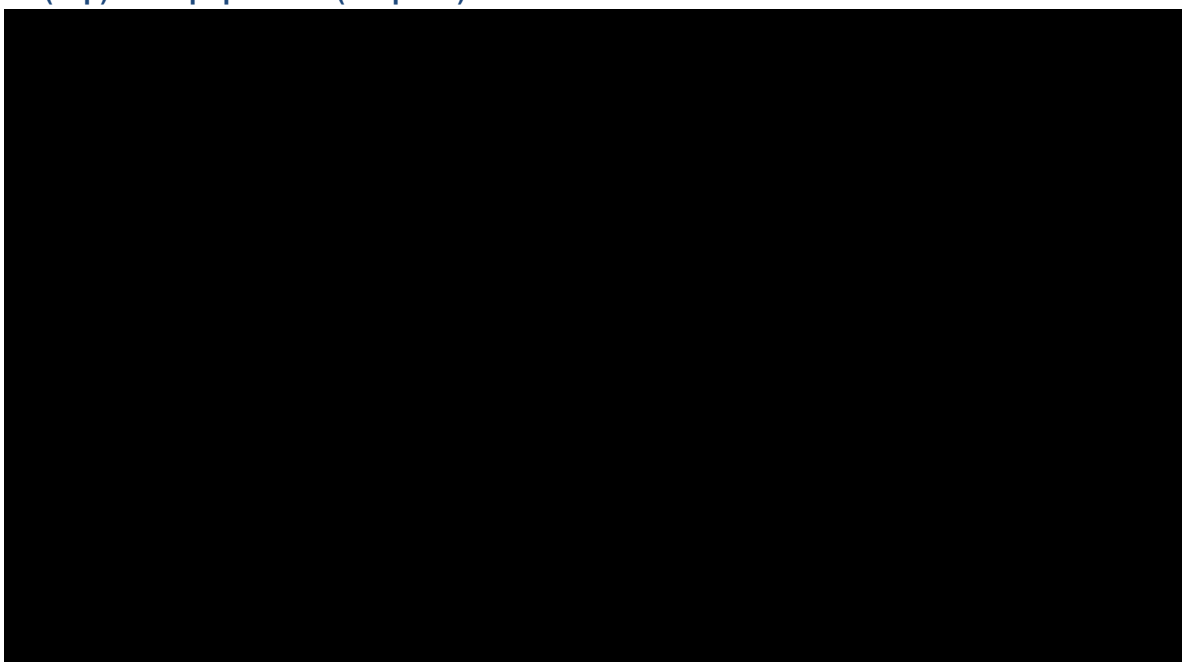
Non-del(17p)/*TP53* mutation population (VenG versus GClb)

The model results from the PSA are presented in the scatter plot at list price in Figure 30 and at venetoclax PAS price in Figure 31. Similar to the deterministic results, VenG is [redacted] over GClb in the PSA also.

The total cost and QALY estimates are comparable between the deterministic and the probabilistic analyses (differ by [redacted] for incremental total costs at list price and [redacted] at venetoclax PAS price; and [redacted] for QALYs at list price and [redacted] at venetoclax PAS price, due to stochastic variation between model runs).

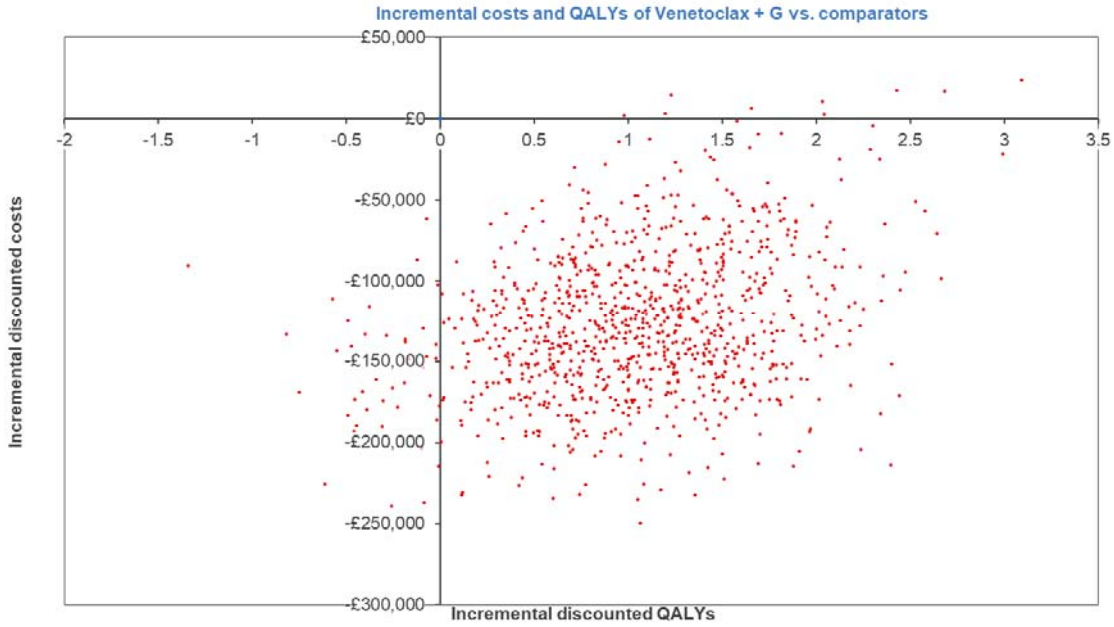
Figure 32 and Figure 33 display the cost-effectiveness acceptability curve at different values of WTP at list price and venetoclax PAS price, respectively. At a £30,000/QALY threshold, VenG has over 90% probability of being cost-effective when compared to GClb.

Figure 30: Scatter plot of probabilistic results on the cost-effectiveness plane for non-del(17p)/*TP53* population (list price)



Abbreviations: QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 31: Scatter plot of probabilistic results on the cost-effectiveness plane for non-del(17p)/*TP53* population (venetoclax PAS price)*



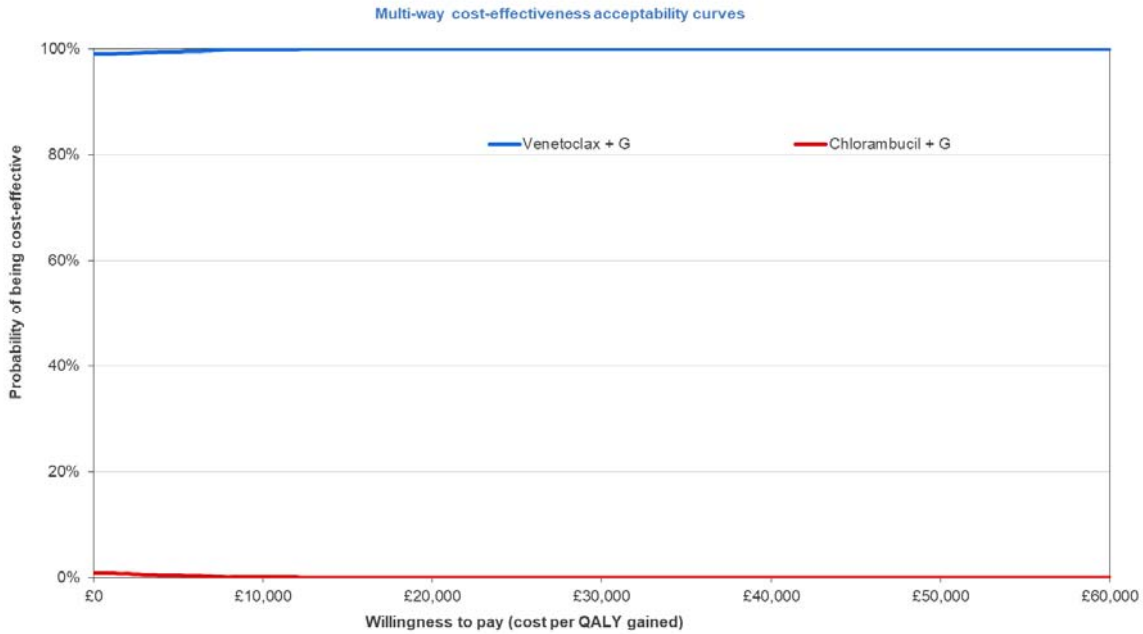
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: PAS: Patient Access Scheme; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 32: Cost-effectiveness acceptability curves for non-del(17p)/*TP53* population (list price)

[redacted]

Abbreviations: Chlorambucil + G: chlorambucil with obinutuzumab; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 33: Cost-effectiveness acceptability curves for non-del(17p)/*TP53* population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: Chlorambucil + G: chlorambucil with obinutuzumab; PAS: Patient Access Scheme; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Del(17p)/*TP53* mutation population (VenG versus ibrutinib)

The model results from the PSA are presented in the scatter plot at list price in Figure 34 and at venetoclax PAS price in Figure 35. Similar to the deterministic results, VenG is [redacted] versus ibrutinib in the PSA also.

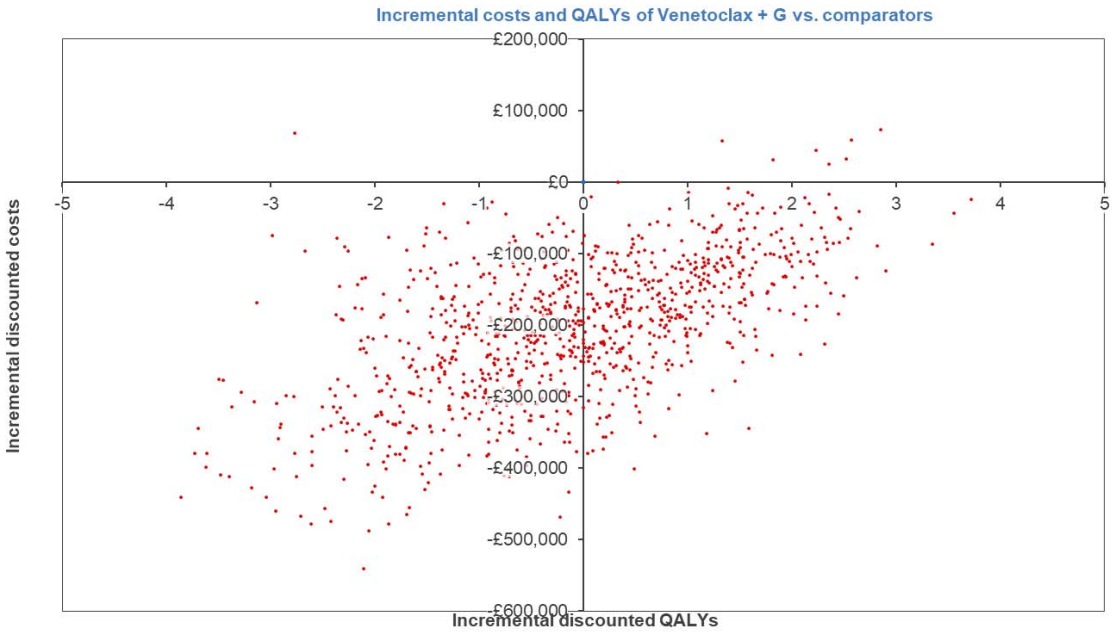
The total cost and QALY estimates are comparable between the deterministic and the probabilistic analyses (differ by [redacted] for incremental total costs at list price and [redacted] at venetoclax PAS price; and [redacted] for QALYs at list price and [redacted] at venetoclax PAS price, however these relative variations [redacted]).

Figure 36 and Figure 37 display the cost-effectiveness acceptability curve at different values of WTP at list price and venetoclax PAS price, respectively. VenG is observed to have a probability of being the cost-effective option of over 95% at a threshold of £30,000 per QALY gained.

Figure 34: Scatter plot of probabilistic results on the cost-effectiveness plane for del(17p)/*TP53* population (list price)

Abbreviations: QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 35: Scatter plot of probabilistic results on the cost-effectiveness plane for del(17p)/*TP53* population (venetoclax PAS price)*

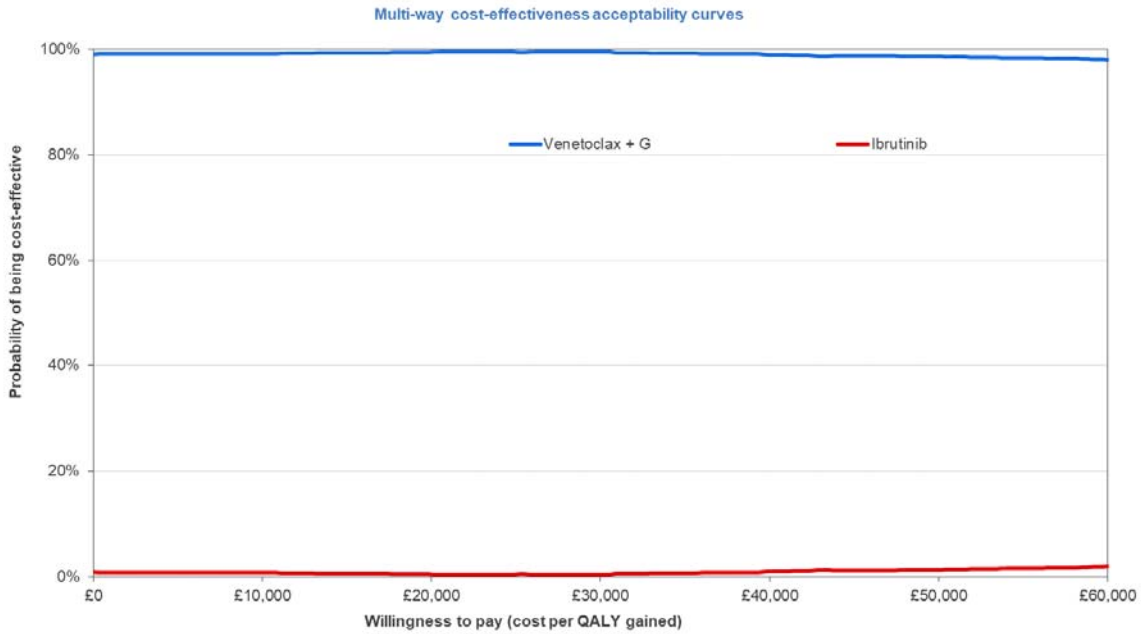


*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: Chlorambucil + G: chlorambucil with obinutuzumab; PAS: Patient Access Scheme; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 36: Cost-effectiveness acceptability curves for del(17p)/*TP53* population (list price)

Abbreviations: QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 37: Cost-effectiveness acceptability curves for del(17p)/*TP53* population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: PAS: Patient Access Scheme; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

A.3.8.2 Deterministic sensitivity analysis

Non-del(17p)/*TP53* mutation population (VenG versus GClb)

Figure 38, Figure 39 and Figure 40 present the tornado plots from the one-way deterministic sensitivity analysis for incremental costs, QALYs and ICER, respectively, for VenG versus GClb at list price. Figure 41, Figure 42 and Figure 43 present the same data at venetoclax PAS price.

In cases where uncertainty data was not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The greatest impact on incremental costs is due to age. The age of patients drives the VenG and GClb survival curves and the survival curves are the key determinant of the incremental costs in the model. The greatest driver of incremental QALYs and of the incremental cost per QALY is the PFS utility following the FTD period value followed by the PPS utility value. Since a large proportion of patients in the VenG arm remain in the PFS following the FTD period compared to GClb, the QALYs accrued in this health state have the largest impact on the cost per QALY.

Figure 38: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus GClb) for non-del(17p)/*TP53* mutation population (list price)

Abbreviations: CT: computed tomography; GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

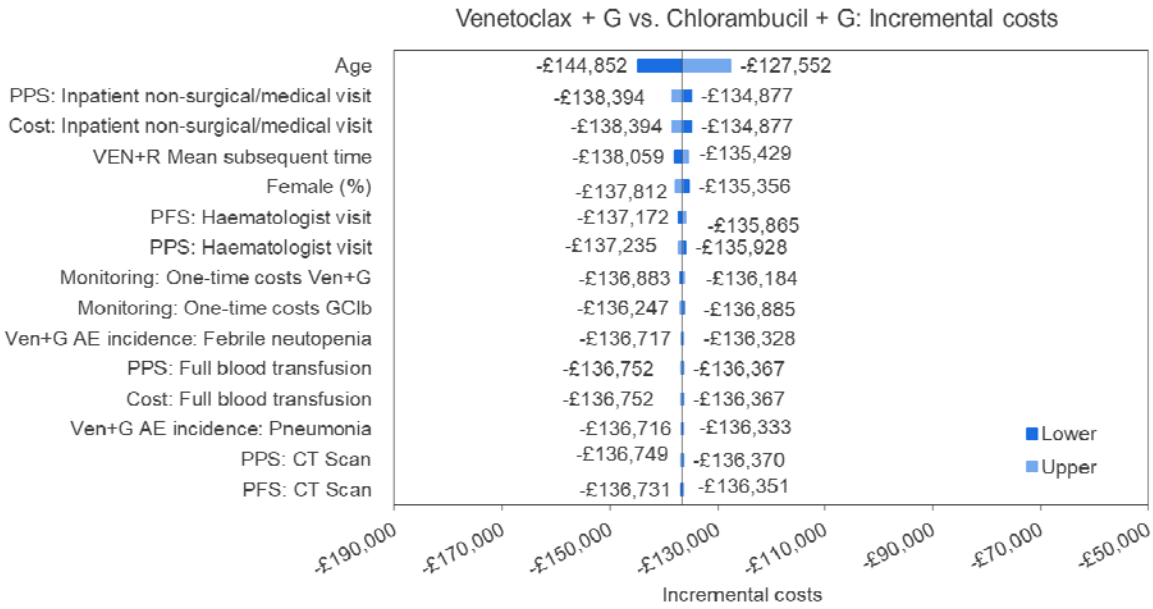
Figure 39: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus GClb) for non-del(17p)/*TP53* mutation population (list price)

Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Figure 40: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus GClb) for non-del(17p)/*TP53* mutation population (list price)

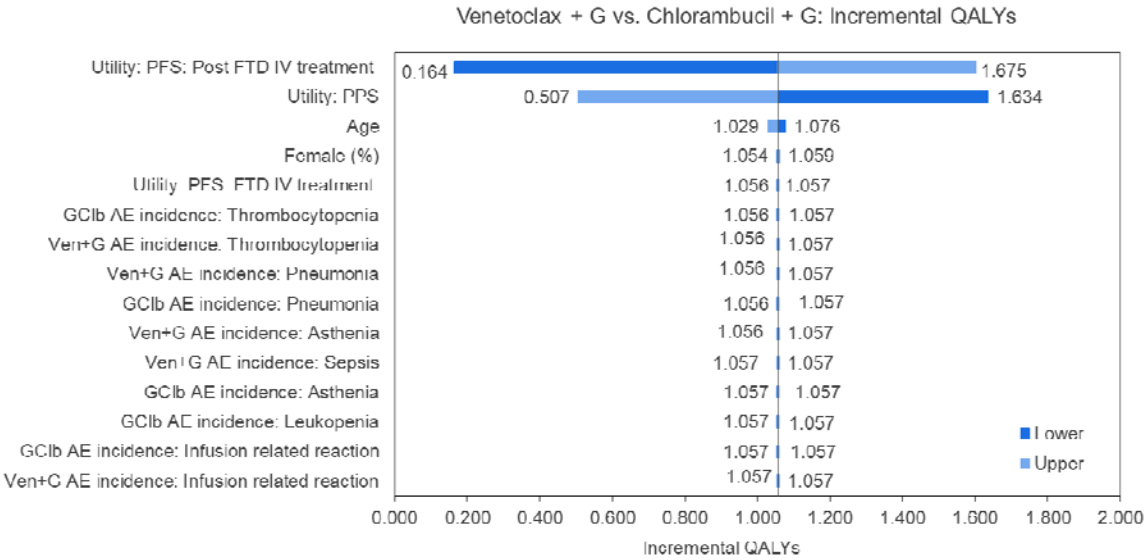
Abbreviations: CT: computed tomography; GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Figure 41: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus GClb) for non-del(17p)/*TP53* mutation population (venetoclax PAS price)*



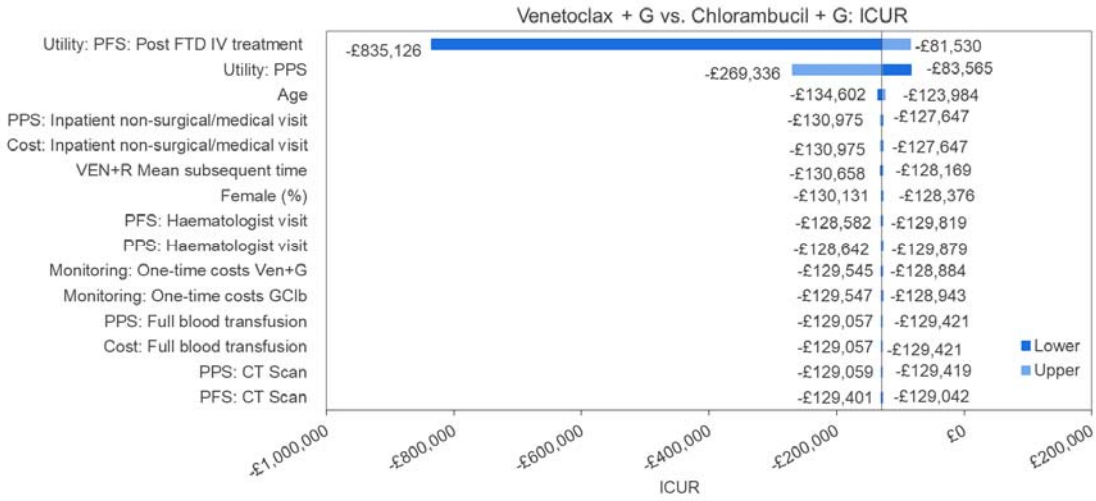
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: CT: computed tomography; GClb: chlorambucil with obinutuzumab; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Figure 42: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus GClb) for non-del(17p)/*TP53* mutation population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: AE: adverse event; GClb: chlorambucil with obinutuzumab; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Figure 43: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus GClb) for non-del(17p)/*TP53* mutation population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: CT: computed tomography; GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; IV: intravenous; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.

Del(17p)/*TP53* mutation population (VenG versus ibrutinib)

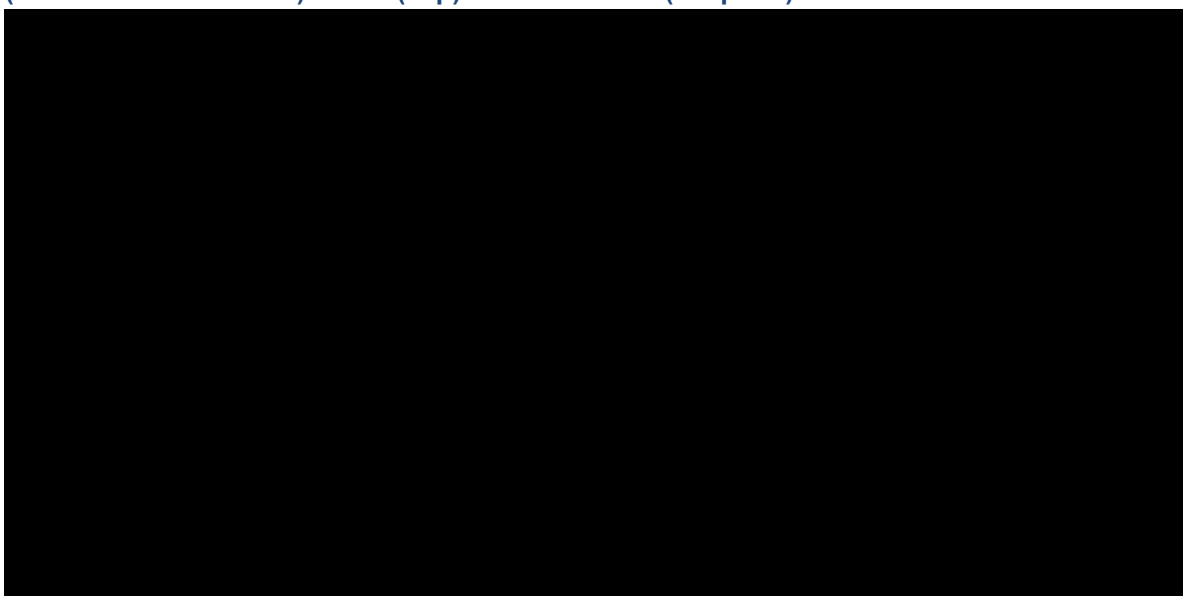
Figure 44, Figure 45 and Figure 46 present the tornado plots from the one-way deterministic sensitivity analysis for incremental costs, QALYs and ICER, respectively, for VenG versus ibrutinib. Figure 47, Figure 48 and Figure 49 present the same data at venetoclax PAS price.

The greatest impact on incremental costs and QALYs is due to the OS HR versus VenG.

Figure 44: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus ibrutinib) for del(17p)/*TP53* mutation (list price)

Abbreviations: AE: adverse event; HR: hazard ratio; Ibr: ibrutinib; IV: intravenous; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

Figure 45: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus ibrutinib) for del(17p)/*TP53* mutation (list price)



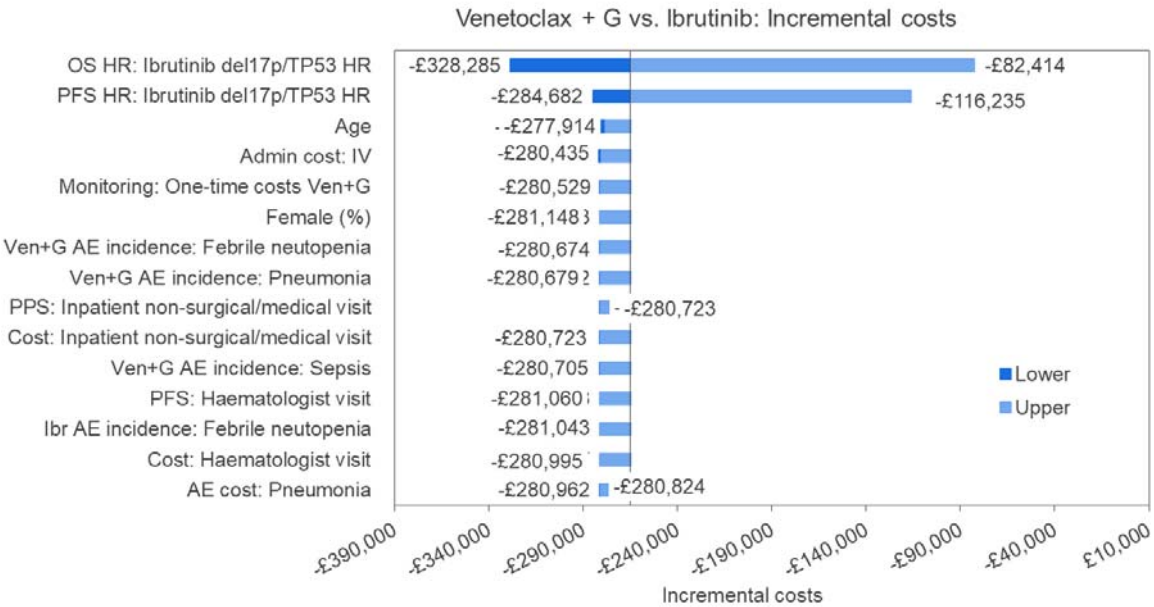
Abbreviations: AE: adverse event; HR: hazard ratio; IV: intravenous; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life-year; VenG: venetoclax with obinutuzumab.

Figure 46: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus ibrutinib) for del(17p)/*TP53* mutation (list price)

[redacted]

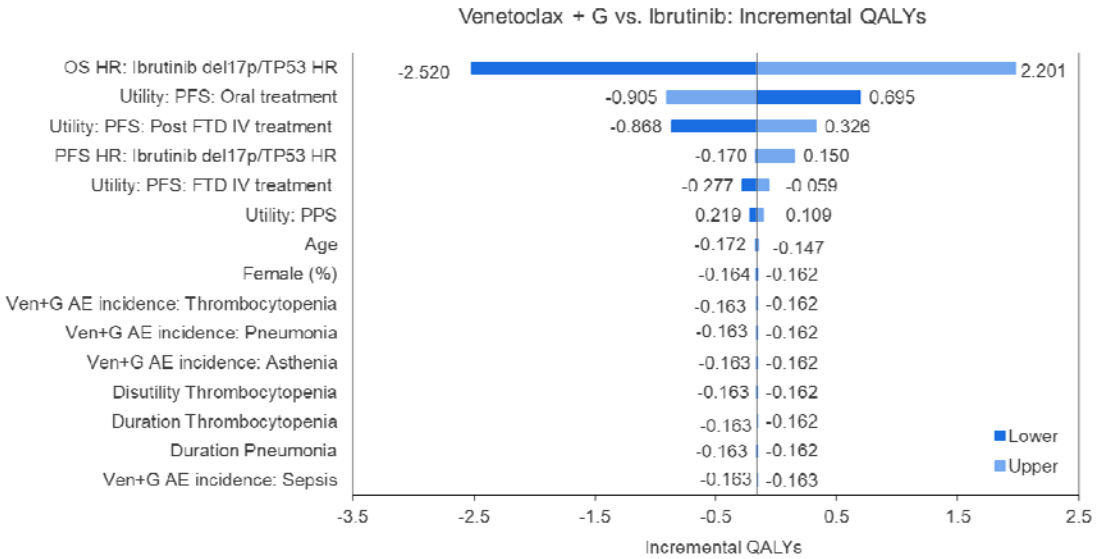
Abbreviations: AE: adverse event; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IV: intravenous; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

Figure 47: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus ibrutinib) for del(17p)/*TP53* mutation population (venetoclax PAS price)*



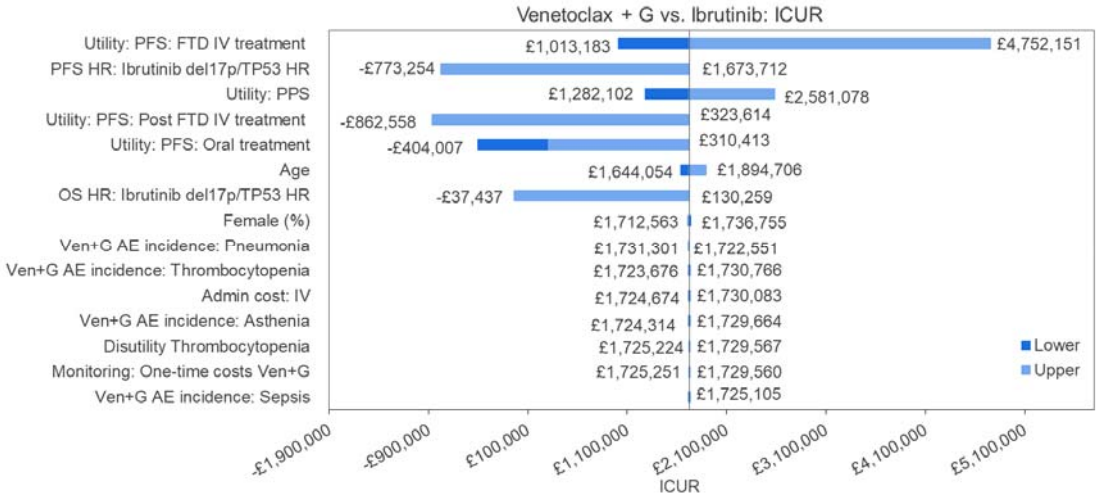
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: AE: adverse event; HR: hazard ratio; Ibr: ibrutinib; IV: intravenous; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

Figure 48: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus ibrutinib) for del(17p)/*TP53* mutation population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: AE: adverse event; HR: hazard ratio; IV: intravenous; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life-year; VenG: venetoclax with obinutuzumab.

Figure 49: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus ibrutinib) for del(17p)/*TP53* mutation population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Notes: IV category refers to intravenous costs.
Abbreviations: AE: adverse event; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IV: intravenous; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

A.3.8.3 Scenario analysis

All the scenarios and their respective descriptions are provided in the original submission (Section B.3.8.3). The scenario analysis results for the treatment comparators in the model are provided in In line with the results in the original submission, removing discounting on QALYs improves the incremental QALY result for VenG. Within the second scenario, which assesses shorter time horizons of 1–5 years, a large impact is observed on model results since VenG accrues fewer incremental QALYs over the shorter time period whilst the majority of VenG costs are captured within the first year. Changing TLS cost or AE rates does not have a large impact on the model while changing utility values has a large impact on the incremental QALYs.

The effect of using alternative distributions for the OS dependent survival model (assuming either no treatment effect or treatment effect) does not lead to large changes in incremental results.

Applying the PPS data from the CLL11 trial has a significant impact (NMB at a £30,000/QALY threshold: 82% lower compared to base case) on the increment cost and QALYs versus GClb. However, VenG remains dominant over GClb due to OS being close to background mortality. Compared to the CLL11 scenario, the RESONATE (NMB: 21% lower compared to base case) and Warwick ERG NMA scenarios (NMB: 0.019% lower compared to base case) have a less significant impact on cost and QALYs since the OS curves generated from these scenarios are closer to the CLL14 results than the ones generated using the CLL11 scenario.

Table 40 for the non-del(17)/*TP53* population and in Table 41 for the del(17p)/*TP53* population.

Non-del(17p)/*TP53* mutation population (VenG versus GClb)

In line with the results in the original submission, removing discounting on QALYs improves the incremental QALY result for VenG. Within the second scenario, which assesses shorter time horizons of 1–5 years, a large impact is observed on model results since VenG accrues fewer incremental QALYs over the shorter time period whilst the majority of VenG costs are captured within the first year. Changing TLS cost or AE rates does not have a large impact on the model while changing utility values has a large impact on the incremental QALYs.

The effect of using alternative distributions for the OS dependent survival model (assuming either no treatment effect or treatment effect) does not lead to large changes in incremental results.

Applying the PPS data from the CLL11 trial has a significant impact (NMB at a £30,000/QALY threshold: 82% lower compared to base case) on the increment cost and QALYs versus GClb. However, VenG remains dominant over GClb due to OS being close to background mortality. Compared to the CLL11 scenario, the RESONATE (NMB: 21% lower compared to base case) and Warwick ERG NMA scenarios (NMB: 0.019% lower compared to base case) have a less significant impact on cost and QALYs since the OS curves generated from these scenarios are closer to the CLL14 results than the ones generated using the CLL11 scenario.

Table 40: Scenario analysis for non-del(17p)/*TP53* mutation population

	List price			
	Incremental costs, £	Incremental QALYs	Incremental LYs	ICER, £/QALY
Base case	[redacted]	1.057	0.000	Dominant
Discount rate. Costs: 0%, QALYs: 0%	[redacted]	1.479	0.000	Dominant
Discount rate. Costs: 0%, QALYs: 6%	[redacted]	0.854	0.000	Dominant
Discount rate. Costs: 6%, QALYs: 6%	[redacted]	0.854	0.000	Dominant
Discount rate. Costs: 6%, QALYs: 0%	[redacted]	1.479	0.000	Dominant
Time horizon: 5 year	[redacted]	0.222	0.000	[redacted]
Time horizon: 10 year	[redacted]	0.608	0.000	Dominant
Time horizon: 15 year	[redacted]	0.870	0.000	Dominant
Time horizon: 25 year	[redacted]	1.048	0.000	Dominant
TLS prophylaxis cost halved	[redacted]	1.057	0.000	Dominant
TLS prophylaxis cost doubled	[redacted]	1.057	0.000	Dominant
TLS prophylaxis cost removed	[redacted]	1.057	0.000	Dominant
AE rates halved	[redacted]	1.057	0.000	Dominant
AE rates doubled	[redacted]	1.056	0.000	Dominant
AEs removed	[redacted]	1.057	0.000	Dominant
Utility (from CLL14 trial) Pre−progression utility = 0.829	[redacted]	1.101	0.000	Dominant
Utility from Venetoclax monotherapy submission (pre−progression utility = 0.748; EQ−5D data study 116)	[redacted]	0.711	0.000	Dominant
CLL11	[redacted]	0.690	0.000	Dominant
RESONATE	[redacted]	1.048	0.000	Dominant
Warwick ERG – NMA	[redacted]	1.055	0.000	Dominant
Subsequent treatment scenarios				
Scenario 1	[redacted]	1.057	0.000	Dominant
Scenario 2	[redacted]	1.057	0.000	Dominant
Scenario 3	[redacted]	1.057	0.000	Dominant
Scenario 4	[redacted]	1.057	0.000	Dominant
Wastage cost removed	[redacted]	1.057	0.000	Dominant
Excess risk of 90% added to background mortality to generate VenG survival of 80% at 5 years	[redacted]	0.886	0.000	Dominant
10% excess risk of death to landmark	[redacted]	1.036	0.000	Dominant
15% excess risk of death to landmark	[redacted]	1.026	0.000	Dominant
19% excess risk of death to landmark	[redacted]	1.018	0.000	Dominant
OS and PFS scenarios				

OS distribution – no treatment effect Exponential	[redacted]	1.057	0.000	Dominant
OS distribution – no treatment effect Generalised gamma	[redacted]	1.055	0.000	Dominant
OS distribution – No treatment effect Gompertz	[redacted]	0.989	0.000	Dominant
OS distribution – No treatment effect Log−logistic	[redacted]	1.056	0.000	Dominant
OS distribution – No treatment effect Log−normal	[redacted]	1.055	0.000	Dominant
OS distribution – No treatment effect Weibull	[redacted]	1.056	0.000	Dominant
OS distribution – No treatment effect Hazard Spline (1 knot)	[redacted]	1.056	0.000	Dominant
OS distribution – No treatment effect Hazard Spline (2 knots)	[redacted]	1.057	0.000	Dominant
OS distribution – No treatment effect Hazard Spline (3 knots)	[redacted]	1.057	0.000	Dominant
OS distribution – No treatment effect Odds Spline (1 knot)	[redacted]	1.056	0.000	Dominant
OS distribution – No treatment effect Odds Spline (2 knots)	[redacted]	1.057	0.000	Dominant
OS distribution – No treatment effect Odds Spline (3 knots)	[redacted]	1.057	0.000	Dominant
OS distribution – No treatment effect Probit Spline (1 knot)	[redacted]	1.055	0.000	Dominant
OS distribution – No treatment effect Probit Spline (2 knots)	[redacted]	1.056	0.000	Dominant
OS distribution – No treatment effect Probit Spline (3 knots)	[redacted]	1.056	0.000	Dominant
PFS −Independent Models Exponential	[redacted]	1.009	0.000	Dominant
PFS −Independent Models Generalised Gamma	[redacted]	0.742	0.000	Dominant
PFS −Independent Models Gompertz	[redacted]	0.546	0.000	Dominant
PFS −Independent Models Log−logistic	[redacted]	1.057	0.000	Dominant
PFS −Independent Models Log−normal	[redacted]	1.135	0.000	Dominant
PFS −Independent Models Weibull	[redacted]	1.068	0.000	Dominant
PFS −Independent Models	[redacted]	0.882	0.000	Dominant

Hazard Spline (1 knot)				
PFS −Independent Models Hazard Spline (2 knots)	[redacted]	0.587	0.000	Dominant
PFS −Independent Models Hazard Spline (3 knots)	[redacted]	0.590	0.000	Dominant
PFS −Independent Models Odds Spline (1 knot)	[redacted]	0.939	0.000	Dominant
PFS −Independent Models Odds Spline (2 knots)	[redacted]	0.674	0.000	Dominant
PFS −Independent Models Odds Spline (3 knots)	[redacted]	0.724	0.000	Dominant
PFS −Dependent Models Exponential	[redacted]	0.983	0.000	Dominant
PFS −Dependent Models Generalised Gamma	[redacted]	0.717	0.000	Dominant
PFS −Dependent Models Gompertz	[redacted]	0.391	0.000	Dominant
PFS −Dependent Models Log−logistic	[redacted]	0.695	0.000	Dominant
PFS −Dependent Models Log−normal	[redacted]	0.650	0.000	Dominant
PFS −Dependent Models Weibull	[redacted]	0.713	0.000	Dominant
PFS −Dependent Models Hazard Spline (1 knot)	[redacted]	0.673	0.000	Dominant
PFS −Dependent Models Hazard Spline (2 knots)	[redacted]	0.697	0.000	Dominant
PFS −Dependent Models Hazard Spline (3 knots)	[redacted]	0.479	0.000	Dominant
PFS −Dependent Models Odds Spline (1 knot)	[redacted]	0.643	0.000	Dominant
PFS −Dependent Models Odds Spline (2 knots)	[redacted]	0.636	0.000	Dominant
PFS −Dependent Models Odds Spline (3 knots)	[redacted]	0.469	0.000	Dominant
PFS −Dependent Models Probit Spline (1 knot)	[redacted]	0.565	0.000	Dominant
PFS −Dependent Models Probit Spline (2 knots)	[redacted]	0.553	0.000	Dominant
PFS −Dependent Models Probit Spline (3 knots)	[redacted]	0.415	0.000	Dominant
Extreme scenario: Using lowest NMB generated from	[redacted]	0.392	0.000	Dominant

the curves above: **PFS −Dependent Models Gompertz (NMB = £162,963)** **OS distribution – No Treatment effect Gompertz (NMB = £130,017)**				

Abbreviations: AE: adverse event; ERG: Evidence Review Group; EQ-5D: EuroQol-5D; GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; LY: life year; NMA: network meta-analysis; NMB: net monetary benefit; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALY: quality-adjusted life-year; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.

Del(17p)/*TP53* mutation population (VenG versus ibrutinib)

All scenarios from the list of scenarios described in Section B.3.8.3 (Table 69) of the original submission were applied and Table 71 of original submission was updated using newer CLL14 data cut-off along with assessment of an additional HR from the naïve comparisons:

- Ahn. et al. study (see Section A.2.10.2)[1]
- Assuming equal treatment effect

Using Ahn et al.[1] as a source of ibrutinib efficacy results in ibrutinib accruing higher QALYs and higher costs compared to VenG. This can be translated into VenG being a less effective and far less costly treatment option but still cost-effective, as per NMB values generated, for patients with del(17p)/*TP53* mutation for whom limited treatments are available. Moreover, on seeking advice from UK clinicians, the complete paucity of evidence for first-line CLL ibrutinib use in this population was stressed. The advice received was that no reliable conclusions can be drawn on the long-term efficacy of VenG versus ibrutinib. Therefore, a scenario of equivalent efficacy should be considered to enable decision making on the cost effectiveness of VenG versus ibrutinib monotherapy in the del(17p)/*TP53* mutation population.

VenG was associated with lower costs and lower QALYs resulting in a positive NMB, at a £30,000/QALY threshold, in all but two scenarios (equivalent OS and PFS assumption and 5-year time horizon) where VenG was dominant versus ibrutinib.

Table 41: Scenario analysis for del(17p)/*TP53* mutation population

	List price				
	Incremental costs, £	**Incremental QALYs**	**Incremental LYs**	**ICER, £/QALY**	**NMB, £***
Base case (Mato et al. [2018] HR)	[redacted]	−0.163	−1.069	[redacted]	[redacted]
HR (Ahn et al. [2018])	[redacted]	−2.249	−5.802	[redacted]	[redacted]
Equal efficacy **PFS HR = 1** **OS HR = 1** **AE disutility = 0**	[redacted]	0.381	0.000	Dominant	[redacted]
Discount rate. Costs: 0%, QALYs: 0%	[redacted]	−0.273	−1.069	[redacted]	[redacted]
Discount rate. Costs: 0%,	[redacted]	−0.114	−1.069	[redacted]	[redacted]

QALYs: 6%					
Discount rate. Costs: 6%, QALYs: 6%	[redacted]	−0.114	−1.069	[redacted]	[redacted]
Discount rate. Costs: 6%, QALYs: 0%	[redacted]	−0.273	−1.069	[redacted]	[redacted]
Time horizon: 5 year	[redacted]	0.041	−0.191	Dominant	[redacted]
Time horizon: 10 year	[redacted]	−0.032	−0.502	[redacted]	[redacted]
Time horizon: 15 year	[redacted]	−0.095	−0.765	[redacted]	[redacted]
Time horizon: 25 year	[redacted]	−0.158	−1.043	[redacted]	[redacted]
TLS prophylaxis cost halved	[redacted]	−0.163	−1.069	[redacted]	[redacted]
TLS prophylaxis cost doubled	[redacted]	−0.163	−1.069	[redacted]	[redacted]
TLS prophylaxis cost removed	[redacted]	−0.163	−1.069	[redacted]	[redacted]
AE rates halved	[redacted]	−0.161	−1.069	[redacted]	[redacted]
AE rates doubled	[redacted]	−0.165	−1.069	[redacted]	[redacted]
AEs removed	[redacted]	−0.160	−1.069	[redacted]	[redacted]
Utility (from CLL14 trial) Pre−progression utility = 0.829	[redacted]	−0.685	−1.069	[redacted]	[redacted]
Utility from Venetoclax monotherapy submission (pre−progression utility = 0.748; EQ−5D data study 116)	[redacted]	−0.591	−1.069	[redacted]	[redacted]
Wastage cost removed	[redacted]	N/A	N/A	[redacted]	[redacted]
PFS −Independent Models Exponential	[redacted]	−0.269	−1.069	[redacted]	[redacted]
PFS −Independent Models Generalised Gamma	[redacted]	−0.277	−1.069	[redacted]	[redacted]
PFS −Independent Models Gompertz	[redacted]	−0.281	−1.069	[redacted]	[redacted]
PFS −Independent Models Log−logistic	[redacted]	−0.163	−1.069	[redacted]	[redacted]
PFS −Independent Models Log−normal	[redacted]	−0.133	−1.069	[redacted]	[redacted]
PFS −Independent Models Weibull	[redacted]	−0.280	−1.069	[redacted]	[redacted]
PFS −Independent Models Hazard Spline (1 knot)	[redacted]	−0.279	−1.069	[redacted]	[redacted]
PFS −Independent Models Hazard Spline (2 knots)	[redacted]	−0.286	−1.069	[redacted]	[redacted]
PFS −Independent Models	[redacted]	−0.288	−1.069	[redacted]	[redacted]

Hazard Spline (3 knots)					
PFS −Independent Models Odds Spline (1 knot)	[redacted]	−0.218	−1.069	[redacted]	[redacted]
PFS −Independent Models Odds Spline (2 knots)	[redacted]	−0.291	−1.069	[redacted]	[redacted]
PFS −Independent Models Odds Spline (3 knots)	[redacted]	−0.298	−1.069	[redacted]	[redacted]
PFS −Independent Models Probit Spline (1 knot)	[redacted]	−0.165	−1.069	[redacted]	[redacted]
PFS −Independent Models Probit Spline (2 knots)	[redacted]	−0.283	−1.069	[redacted]	[redacted]
PFS −Independent Models Probit Spline (3 knots)	[redacted]	−0.291	−1.069	[redacted]	[redacted]
PFS −Dependent Models Exponential	[redacted]	−0.209	−1.069	[redacted]	[redacted]
PFS −Dependent Models Generalised Gamma	[redacted]	−0.281	−1.069	[redacted]	[redacted]
PFS −Dependent Models Gompertz	[redacted]	−0.275	−1.069	[redacted]	[redacted]
PFS −Dependent Models Log−logistic	[redacted]	−0.317	−1.069	[redacted]	[redacted]
PFS −Dependent Models Log−normal	[redacted]	−0.332	−1.069	[redacted]	[redacted]
PFS −Dependent Models Weibull	[redacted]	−0.279	−1.069	[redacted]	[redacted]
PFS −Dependent Models Hazard Spline (1 knot)	[redacted]	−0.279	−1.069	[redacted]	[redacted]
PFS −Dependent Models Hazard Spline (2 knots)	[redacted]	−0.279	−1.069	[redacted]	[redacted]
PFS −Dependent Models Hazard Spline (3 knots)	[redacted]	−0.289	−1.069	[redacted]	[redacted]
PFS −Dependent Models Odds Spline (1 knot)	[redacted]	−0.323	−1.069	[redacted]	[redacted]
PFS −Dependent Models Odds Spline (2 knots)	[redacted]	−0.323	−1.069	[redacted]	[redacted]
PFS −Dependent Models Odds Spline (3 knots)	[redacted]	−0.336	−1.069	[redacted]	[redacted]
PFS −Dependent Models Probit Spline (1 knot)	[redacted]	−0.338	−1.069	[redacted]	[redacted]
PFS −Dependent Models Probit Spline (2 knots)	[redacted]	−0.328	−1.069	[redacted]	[redacted]
PFS −Dependent Models Probit Spline (3 knots)	[redacted]	−0.333	−1.069	[redacted]	[redacted]

OS distribution – Treatment effect Generalised Gamma	[redacted]	−0.121	−0.808	[redacted]	[redacted]
OS distribution – Treatment effect Gompertz	[redacted]	−0.218	−1.154	[redacted]	[redacted]
OS distribution – Treatment effect Log−logistic	[redacted]	−0.183	−1.021	[redacted]	[redacted]
OS distribution – Treatment effect Log−normal	[redacted]	−0.156	−0.935	[redacted]	[redacted]
OS distribution – Treatment effect Weibull	[redacted]	−0.221	−1.150	[redacted]	[redacted]
OS distribution – Treatment effect Hazard Spline (1 knot)	[redacted]	−0.223	−1.154	[redacted]	[redacted]
OS distribution – Treatment effect Hazard Spline (2 knots)	[redacted]	−0.162	−1.045	[redacted]	[redacted]
OS distribution – Treatment effect Hazard Spline (3 knots)	[redacted]	−0.157	−1.026	[redacted]	[redacted]
OS distribution – Treatment effect Odds Spline (1 knot)	[redacted]	−0.191	−1.044	[redacted]	[redacted]
OS distribution – Treatment effect Odds Spline (2 knots)	[redacted]	−0.212	−1.113	[redacted]	[redacted]
OS distribution – Treatment effect Odds Spline (3 knots)	[redacted]	−0.212	−1.115	[redacted]	[redacted]
OS distribution – Treatment effect Probit Spline (1 knot)	[redacted]	−0.171	−0.974	[redacted]	[redacted]
OS distribution – Treatment effect Probit Spline (2 knots)	[redacted]	−0.209	−1.088	[redacted]	[redacted]
OS distribution – Treatment effect Probit Spline (3 knots)	[redacted]	−0.212	−1.092	[redacted]	[redacted]
Extreme value testing using lower HR bounds	[redacted]	−2.863	−7.226	[redacted]	[redacted]

from Mato calculation (PFS HR = 0.270 and OS HR = 0.301; VenG least effective eventuality)					
Extreme scenario: OS distribution – Treatment effect Generalised Gamma (NMB = £182,829) PFS – Dependent Models Gompertz (NMB: £113,883)	[redacted]	−0.198	−0.808	[redacted]	[redacted]
Subsequent treatment scenario 2a (VenG subsequent treatment 50% Ibrutinib 50%VenR)	[redacted]	−0.163	−1.069	[redacted]	[redacted]
Subsequent treatment scenario 2b (Ibrutinib subsequent treatment 50% VenR and 50% Vmono)	[redacted]	−0.163	−1.069	[redacted]	[redacted]

*NMB at a £30,000/QALY threshold.
Abbreviations: AE: adverse event; ERG: Evidence Review Group; EQ-5D: EuroQol-5D; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LY: life year; NMA: network meta-analysis; NMB: net monetary benefit; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival; QALY: quality-adjusted life-year; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab; Vmono: venetoclax monotherapy.

A.3.8.4 Summary of sensitivity analyses results

The base case average probabilistic ICER is closely aligned with the base case deterministic ICER for both populations. At the £30,000/QALY threshold typically applied in NICE appraisals, VenG was found to have a greater than 90% probability of being the cost-effective option in the base case, in both the non-del(17p)/*TP53* and del(17p)/*TP53* populations.

The scenario analyses in the non-del(17p)/*TP53* mutation population demonstrated that VenG is consistently dominant when compared to GClb with all but one scenario (5-year time horizon). In the del(17p)/*TP53* mutation population, VenG was dominant versus ibrutinib in two scenarios (5-year time horizon and assuming equal efficacy for OS and PFS). All other scenarios tested demonstrated that the comparison of VenG versus ibrutinib resulted in a positive NMB and the conclusion that VenG is a cost-effective treatment option across all tested scenarios.

A.4 Interpretation and conclusions of the evidence

There are limited treatment options available for untreated CLL, with even fewer options for patients with del(17p)/*TP53* mutation compared to those without del(17p)/*TP53* mutation. Chlorambucil-based chemo-immunotherapies are the backbone of treatment in FCR/BR-unsuitable patients without del(17p)/*TP53* mutation, however there is an unmet need for a broader range of therapeutic options with a different mechanism of action.[13] While B-cell receptor inhibitors such as ibrutinib have reduced the reliance on toxic chemotherapy-based therapies in the previously untreated del(17p)/*TP53* population, there is an unmet need for patients who cannot tolerate ibrutinib, for

instance those with cardiac risk factors or bleeding risk.[13] The high unmet need of CLL patients is further compounded by the fact that CLL patients tend to be older than 70 years (median age at diagnosis is 72 years) and often have clinically relevant coexisting conditions, which limit the extent to which currently available therapies can be used.[4, 24, 25]

Venetoclax is a first-in-class, oral, selective inhibitor of B-cell lymphoma 2 with a unique targeted mechanism of action that distinguishes it from other available therapies. The updated data cut of the CLL14 trial demonstrates that VenG, a chemotherapy-free regimen, has the potential to meet the high unmet need in CLL by offering a highly effective treatment with deep responses and a safety profile that is acceptable, predictable and generally consistent with the known safety profiles of venetoclax and obinutuzumab as single agents.

In the non-del(17p)/*TP53* population, the economic model outcomes suggest that at 5 years VenG is associated with keeping more people in the PFS state, which translates into maintaining a higher level of HRQoL for longer while incurring lower costs of subsequent treatment, relapse and healthcare resource utilisation for the NHS. As such, VenG was found to be dominant in the model and represents a cost-effective use of NHS resources. For the del(17p)/*TP53* population, VenG presents an effective and cost-saving option compared to ibrutinib where treatment costs are incurred until progression. Therefore, VenG represents a cost-effective option in this hard to treat population.

In conclusion, the CLL14 trial provides evidence that VenG can increase the range of effective treatment options available to treat CLL in both patients with and without del(17p)/*TP53* mutation, providing a valuable alternative to current first-line treatment options. Furthermore, VenG has the potential to provide substantial health-related benefits in the form of a fixed-treatment duration chemotherapy-free treatment, with a manageable side effect profile. This enables a significant proportion of patients prolonged time without therapy, reducing the overall burden of treatment.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Clarification questions

December 2019

File name	Version	Contains confidential information	Date
1. ID1402 [ACIC]_VenG_Clarification Q Response_	**FINAL**	**Yes**	**5th Dec 2019**

CONTENTS

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General comment

Please note that for all the analyses in this document, a new model version has been created which contains utility values specific to the treatment mode of administration for the PFS health state but also a separate value for when the patient is off-treatment and in the pre-progression state (i.e. a change compared to the model submitted to NICE on 29th October 2019). This edit was made to optimise modelling of the pre-progression health state using the most reliable, available source of evidence, TA343.[1]

The new model version also generates tornado diagrams for the one-way sensitivity analysis that present the results quantified as net monetary benefit (NMB) at the £30,000 per QALY willingness to pay threshold. This change was made to aid interpretation of results where ICER values are located outside the north-east quadrant of the cost effectiveness plane, for which NMB is a more intuitive summary statistic than ICER.

Section A: Clarification on effectiveness data

A1. Please provide details of the comorbidities related to the unsuitability of FCR and BR for the patient population in the submission.

Due to the age distribution of CLL, two-thirds of patients are likely to have at least one significant co-morbidity and higher risk disease that could impact their suitability for chemotherapy such as FCR and BR (see section B.1.3.4 of the CS). As a result, an assessment of suitability is required prior to initiating chemotherapy. Unfortunately, according to the BSH guidelines, the optimal strategy to determine suitability for chemotherapy remains undetermined and there is no agreement on the use of a specific formal co-morbidity assessment tool. In routine clinical practice, assessment of suitability includes factors such as age, presence and severity of comorbidities and performance status.

The CLL14 trial eligibility criteria included patient characteristics (e.g. coexisting conditions, cumulative illness rating scale [CIRS] score >6 – see full eligibility criteria in CS) that would typically make them unsuitable for FCR and BR. However, as explained above, the decision on individual patient eligibility is a clinical decision which considers a host of factors.

Table 1 provides a breakdown of the concurrent medical condition at baseline of all CLL14 trial participants. A concurrent medical condition at baseline was reported in all patients apart from 1 in the GClb arm.

Table 1. CLL14 trial participants: concurrent medical history

	GClb (N=216)	VenG (N=216)
Total number of patients with at least one condition (%)	[redacted]	[redacted]
Overall total number of conditions	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Congenital, familial and genetic disorders	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]

	GClb (N=216)	VenG (N=216)
Eye disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

A2. On CS page 31 please can you explain what happened to the 12 run-in patients, were they entered into the trial and if so, how (i.e. did they remain in the venetoclax arm or were they randomised)?

A total of 432 patients were randomised (216 in the GClb arm and 216 in the VenG arm). The information presented in the CS pertains to the main randomisation phase only. The 12 patients who received VenG during the safety run-in were not included in the main randomisation phase, and therefore are not part of the venetoclax arm in the main analysis.

A3. For completeness, please confirm that 'TP53 deletion and/or mutation' in Table 9, Table 22 and Figure 15 refers to people with a 17P deletion and/or TP53 mutation. Please provide the number of patients in each arm who have <u>both</u> 17P deletion and TP53 mutation.

We can confirm that the description 'TP53 deletion and/or mutation' in Table 9, Table 22 and Figure 15 does indeed refer to people with a 17p deletion and/or *TP53* mutation.

A total of [redacted] patients in CLL14 had del(17p) and/or *TP53* mutation: [redacted] in the GClb arm and [redacted] in the VenG arm.

A4. PRIORITY: Figure 15 presents subgroup data for 46 people with del(17p)/TP53 mutation present and 287 people with del(17p)/TP53 mutation not present.

- **Please explain why data are missing for the remaining 99 trial participants.**
- **For completeness, please provide subgroup analysis of PFS, OS and ORR for these 99 participants.**
- **Please provide subgroup analysis of OS and ORR for the 287 people with del(17p)/TP53 mutation not present.**
- **Please provide baseline characteristics per treatment arm for:**
  - **the 287 people with del(17p)/TP53 mutation not present**
  - **the 99 participants with missing data**

A corrigendum to the original CSR was recently released and is now included as an attachment to this response document. As noted in the corrigendum:

- The CSR has already been submitted in a number of countries worldwide and since the errors are considered minor with no impact on Benefit/Risk profile, an updated CSR has not been provided, but to ensure transparency, the minor errors are highlighted and corrected outputs are provided within this corrigendum.
- In the published CSR, a minor data error was identified with the outputs concerning the patients in the TP53 status subgroup. Subsequently, the Clinical Overview and Summary of Clinical Efficacy and Summary of Clinical Safety contained this data error: 101 patients with unmutated TP53 status were inadvertently summarised in the 'Unknown' TP53 category. The programming has been corrected in order to account for the mutation/deletions identified through the next generation sequencing (NGS) analysis. This change affects both the TP53 variable, and the TP53 data in the "TP53 mutated and/or 17p deletion" variable.
- The baseline data remain balanced between treatment groups and the subgroup analysis conclusions remain unchanged, namely: the VenG arm showed consistent treatment effect across all pre-specified subgroups, including high-risk patients, which were also consistent with the primary analysis.

For clarity, the correct breakdown of patients by del(17p)/*TP53* status is shown in Table 2.

Table 2: Subgroup population numbers from CLL14

Mutational status	GClb (n=216)	VenG (n=216)	Total (n=432)
Non-del(17p)/*TP53* mutation	[redacted]	[redacted]	[redacted]
Del(17p)/*TP53* mutation	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

The tables provided in the supplementary reference pack ('[A4] AbbVie Data on File_Subgroup Data') contain the baseline characteristics for patients with del(17p)/*TP53* mutation, without del(17p)/*TP53* mutation and for those who are missing data relating to their del(17p)/*TP53* mutation status.

Figure 1–Figure 3 present the IRC-assessed PFS Kaplan–Meier curves for each of the three patient subgroups. Figure 4–Figure 6 present the investigator-assessed Kaplan–Meier curves, and Figure 7–Figure 9 present the OS Kaplan–Meier curves.

Figure 1: IRC assessed PFS for patients with del(17p)/*TP53* mutation

Abbreviations: GClb: chlorambucil with obinutuzumab; IRC: Independent Review Committee; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 2: IRC assessed PFS for patients without del(17p)/*TP53* mutation

Abbreviations: GClb: chlorambucil with obinutuzumab; IRC: Independent Review Committee; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

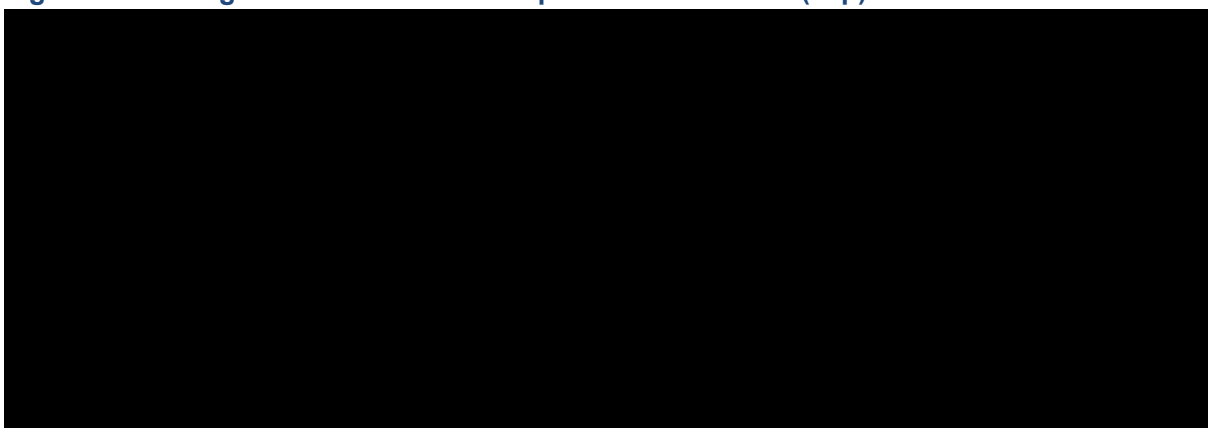
Figure 3: IRC assessed PFS for patients with missing del(17p)/*TP53* mutation status data

Abbreviations: GClb: chlorambucil with obinutuzumab; IRC: Independent Review Committee; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 4: Investigator assessed PFS for patients with del(17p)/*TP53* mutation

Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 5: Investigator assessed PFS for patients without del(17p)/*TP53* mutation



Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 6: Investigator assessed PFS for patients with missing del(17p)/*TP53* mutation status data

Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 7: OS for patients with del(17p)/*TP53* mutation

Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

Figure 8: OS for patients without del(17p)/*TP53* mutation

Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

Figure 9: OS for patients with missing del(17p)/*TP53* mutation status data

Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab.

NB - Any ERG requested subgroup analyses and information on baseline characteristics, specific to the data presented above, could be submitted as part of the sets of analyses that will be repeated using the most recent CLL14 data cut of August 2019.

A5. PRIORITY: Table 32 states there are 386 people with del(17p)/TP53 mutation not present and 0 with this undefined.

- **Please explain the reason for the difference between 386 in this table and the 287 with del(17p)/TP53 mutation not present in Figure 15.**
- **Please explain why there are 14 with 'not defined' in the CEM analysis of Table 32, when the final bullet above the table states none have both missing.**
- **Please explain the difference between the 46 patients in the CSR analysis and 31 patients in the CEM analysis for del(17p)/TP53 mutation.**
- **The ERG accepts it is reasonable to combine mutation status involving del(17p)/TP53 mutation into a single variable. Please explain and justify why different approaches were undertaken in the CSR analysis and CEM analysis and what effect this may have on the results.**

Please refer to the response to Question A4 for the context surrounding this response.

The difference in approaches to combining del(17p)/*TP53* mutation status between the CSR analysis and the CEM analysis is as a result of attempting to provide consistency to previous UK HTA submissions. The programming method used for combining del(17p)/*TP53* mutation status in the CEM analysis is the same as used in the NICE appraisal for venetoclax with rituximab (TA561).[2]

Please note that the final bullet point in the del(17p)/*TP53* coding algorithm stated above Table 32 on Page 80 of CS Document B contains a textual error. In the originally submitted analyses, there were 14 patients for whom their del(17p)/*TP53* mutation status was coded as 'NA' based on the following:

- Del(17p) status = missing AND *TP53* mutation status = missing
- Del(17p) status = missing AND *TP53* mutation status = unknown

As discussed in section B.2.9 of the CS Document B, there is a general paucity of evidence in the del(17p)/*TP53* population across trials in frontline CLL. Therefore, (also considering the small sample sizes under consideration) a change in the approach to combining mutation status involving the del(17p)/*TP53* mutation is not expected to increase the certainty of estimates of efficacy of VenG versus ibrutinib in the del(17p)/*TP53* mutated population.

Figures presented in the CS do not take into account the CSR corrigendum and corresponding changes in defined sample sizes. This could be addressed as part of the updated model and supporting analyses using CLL14 August 2019 cut-off data.

A6. Why are there apparent sharp decreases in the numbers of patients receiving first-line treatment in both arms shortly before the 12-month stopping rule?

The reason why the numbers of patients receiving first-line treatment in both arms decrease shortly before 12 months is because study treatments are administered for 12 cycles and each cycle has 28 days, which corresponds to approximately 11.2 months (assuming each month has 30 days).

A7. Please provide n/N and % for the data presented in Figure 6.

Table 3 and Table 4 present the data shown in Figure 6, Page 48 of the CS Document B for VenG and GClb, respectively.

Table 3: Undetectable MRD in peripheral blood over time for VenG

Timepoint	Undetectable MRD ($<10^4$)	Detectable MRD	PD/Death	Withdrawn	Missing
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C12D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C7D1: Cycle 7, Day 1; C9D1: Cycle 9, Day 1; C12D1: Cycle 12, Day 1; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PD: progressive disease; VenG: venetoclax with obinutuzumab.

Table 4: Undetectable MRD in peripheral blood over time for GClb

Timepoint	Undetectable MRD ($<10^4$)	Detectable MRD	PD/Death	Withdrawn	Missing
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C12D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C7D1: Cycle 7, Day 1; C9D1: Cycle 9, Day 1; C12D1: Cycle 12, Day 1; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PD: progressive disease; VenG: venetoclax with obinutuzumab.

A8. Please provide the group sizes for the Table 18 for completeness.

Table 18 in the CS contained an error. This has been corrected in the following table along with sample sizes

Table 5: (Page 49, Table 18 of CS) Undetectable MRD rates in patients with CR/CRi at EOT assessment

	Undetectable MRD, n (%)*	Detectable MRD, n (%)**	Difference in undetectable MRD rates (95% CI)	p value	OR (95% CI)
Peripheral Blood					

	Undetectable MRD, n (%)*	Detectable MRD, n (%)**	Difference in undetectable MRD rates (95% CI)	p value	OR (95% CI)
VenG (N=107)	91 (85)	16 (15)	23.05 (6.85, 39.24)	0.0012	3.49 (1.6, 7.6)
GClb (N=50)	31 (62)	19 (38)			
Bone Marrow					
VenG (N=107)	73 (68.2)	34 (31.8)	22.2 (4.69, 39.76)	0.0078	2.52 (1.27, 5.02)
GClb (N=50)	23 (46)	27 (54)			

A9. On CS page 52 for the duration of response, how are the numbers who responded (197 and 200) derived? Please explain why these don't match the number with ORR in Figure 5.

Figure 5 on Page 52 of CS Document B shows the overall response rate by Investigator at the end of treatment, in which 154 and 183 responders were included from the GClb and VenG arms, respectively (see **Table *1***Table 6 for breakdown). For the calculation of overall response rate by Investigator at the end of treatment, patients were required to have an Investigator assessment of response within 57 days after last treatment. Results from the Investigator assessment of response on the EOT assessment are included in the calculation of the overall response. Because the EOT assessment day varies per patient, a specific cut-off day after the EOT has been used to include the appropriate visit.In contrast, for the calculation of duration of response, patients were only required to have an Investigator assessment of response at any time during the study. The 60 additional responders (43 from the GClb arm, and 17 from the VenG arm) included in the duration of response analysis had an Investigator assessment of response at a time other than for the EOT assessment. These contribute to the final patient numbers of 200 and 197 for the GClb and VenG group respectively. Therefore, these 60 patients were not included in the overall response calculation at EOT, but they were included in the duration of response calculation.

Table 6: Undetectable MRD in peripheral blood over time for GClb

	Complete Response (CR)	Combined Response* (CR/CRi)	Partial Response (PR) (Partial* Response)	Overall Response Rate (CR + CRi + PR)
VenG (N=216), n (%)	[redacted]	107 (49.5)	76 (35.2)	183 (84.7)
GClb (N=216), n (%)	[redacted]	50 (23.1)	104 (48.2)	154 (71.3)

*Combined response includes patients achieving complete response either with or without complete bone marrow recovery

Abbreviations: CR: complete response; CRi: complete response with incomplete bone marrow recovery; PR: partial response.

A10. On CS page 56 (and Appendix L.3) please provide baseline, FUM24 data and change of baseline data at FUM24 (mean and SD) for all PROs, including EQ-5D index. Why is there a final data point at FUM30 for GClb only?

Baseline, follow-up Month 24 and change in baseline at follow-up Month 24 data are presented in Table 7, Table 8 and Table 9 for MDASI, EORTC QLQ-C30 and EQ-5D-3L respectively.

Table 7: Mean MDASI scores at baseline and follow-up Month 24

	VenG, mean (SD)			GClb, mean (SD)		
	n	Value	Change from Baseline	n	Value	Change from Baseline
Mean core symptom severity score						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean module symptom severity score						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean interference score						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean core symptom severity: Questions 1 to 13 combined (13 items)
Mean module symptom severity: Questions 14 to 19 combined (6 items)
Mean interference (symptom distress): Questions 20 to 25 combined (6 items)
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)[3]

Table 8: EORTC QLQ-C30 reporting by dimension at baseline and follow-up Month 24

	VenG, mean (SD)				GClb, mean (SD)			
	n	Value	n	Change from Baseline	n	Value	n	Change from Baseline
Physical functioning								
Baseline	[redacted]	[redacted]	n/a	n/a	[redacted]	[redacted]	n/a	n/a
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning								
Baseline	[redacted]	[redacted]	n/a	n/a	[redacted]	[redacted]	n/a	n/a
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea								

Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Global health status/QoL								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Physical functioning: Questions 1 to 5 combined (5 items); *Role functioning:* Questions 6 to 7 combined (2 items); *Dyspnoea*: Question 8 (1 item); *Pain:* Questions 9 and 19 combined (2 items); *Fatigue*: Questions 10, 12, 18 combined (3 items); *Insomnia:* Question 11 (1 item); *Appetite loss:* Question 13 (1 item); *Nausea and vomiting:* Questions 14 and 15 combined (2 items); *Constipation:* Question 16 (1 item); *Diarrhoea:* Question 17 (1 item); *Emotional functioning:* Questions 21 to 24 combined (4 items); *Cognitive functioning*: Questions 20 and 25 combined (2 items); *Social functioning:* Questions 26 and 27 combined (2 items); *Financial Difficulties*: Question 28 (1 item); *Global health status/QoL:* Questions 29 and 30 combined (2 items).
Abbreviations: GClb: chlorambucil with obinutuzumab; QoL: quality-of-life; SD: standard deviation; VenG: venetoclax with obinutuzumab.

Table 9: EQ-5D-3L reporting by dimension at baseline and follow-up Month 24

	VenG, mean (SD)				GClb, mean (SD)			
	n	Value	n	Change from Baseline	n	Value	n	Change from Baseline
Utility 1 to 5 score								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Your own health state today								
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility: Questions 1–5 combined, transformed to utility values (5 items)
Your own health state today (visual-analogue scale): Question 6 (1 item)
Abbreviations: EQ-5D-3L: European Quality of Life 5 dimensions 3 level questionnaire; GClc: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.
Source: AbbVie Data on File (CLL14 Clinical Study Report)[3]

The final data point at follow-up Month 30 for the GClb arm includes data from just one patient. As of 17th August 2018, the follow-up time for that patient was 32.2 months. The maximum follow-up time for all 432 patients was 35.9 months. 86 patients (45 in the GClb arm and 31 in the VenG arm) had a follow-up time equal to or greater than 32.2 months, however there are no PRO data available for those patients. No rationale was provided in the dataset for why this data was not recorded.

The compliance data for each PRO measure, along with the full results at each timepoint are provided in the supplementary reference pack ('[A10] AbbVie Data on File_PRO Outcomes'). For transparency, the data for the one patient with successfully reported follow-up Month 30 were included in the submission, despite that for this timepoint, the data are imbalanced between the two treatment arms.

A11. Table 25: summary of patient characteristics in CLL14 and comparator studies. Please justify why 65 years is used as the cut-off in this Table, whilst 75 years is used as the predefined cut-off in the CLL14 subgroup analysis.

CLL14 recruited patients with comorbidities and this inevitably covers older patients (>70 years); this was not a key eligibility criterion in the comparator studies. In CLL14, the cut-off of 75 years of age was selected in order to quantify how age is correlated with comorbidities given the frailty of the CLL14 patient cohort.

Age in the CLL14 trial was assessed alongside age of the comparator trials to evaluate whether alignment of the patient populations was required in terms of fitness (i.e. suitability for chemotherapy) of the patient population, which is highly correlated with age. Patient fitness for chemotherapy was identified as an important prognostic factor and effect modifier. Thus, to ensure the comparability of evidence, the trials included in the naïve indirect comparisons were assessed on fitness for chemotherapy of the patient population, based on criteria derived from the National Comprehensive Cancer Network (NCCN) guidelines. We chose a cut-off of 65 years of age, since this is part of the definition of being an unfit patient for chemotherapy. The second part of the definition of being unfit for chemotherapy includes a CIRS score of 6 or higher, however, none of the comparator trials reported on the CIRS score. Finally, we did not restrict any of the naïve indirect comparisons in the del(17p)/*TP53* mutation subgroup by age since none of the comparator trials provided such information for the del(17p)/*TP53* mutation subgroup of interest. Instead, we used the largest sample size available to increase the robustness of the estimates.

We do appreciate that information in Table 25, Page 64 of CS Document B might have been slightly unclear in interpreting information available from comparator trials on first-line CLL del(17p)/*TP53* mutated patients. Specifically, for the Ahn source, information on age is not on the population of interest and includes relapsed/refractory patients which are outside the scope of this decision problem. The source does not provide age information on treatment naïve patients therefore those values should have been "NR" table entries.

A12. On CS page 86 Table 34: please confirm sample sizes for each group.

The sample sizes for the non-del(17p)/TP53 mutation and del(17p)/TP53 mutation populations used in the model are provided in Table 10.

Table 10: Extension of Table 34 (Page 86) in the CS Document B

Variable	Application in the model	
	Non-del(17p)/*TP53*	Del(17p)/*TP53*
Sample size	[redacted]	[redacted]

A13. Please provide details of second and later lines of treatment received by the UK specific CLL14 patients, by treatment arm and del(17p)/TP53 mutation status. (e.g. what treatments they received and how long they were taken for). Please also provide this information for the whole trial population.

There were eight patients in the CLL14 trial from the UK (1 in the GClb arm and 7 in the VenG arm). None of these patients had progressive disease as of 17th August 2018 and so did not receive another anti-leukaemia therapy.

The listings of the next anti-leukaemia therapy for all of the CLL14 population, along with their del(17p)/*TP53* mutation status, is provided in the supporting references, '[A13] AbbVie Data on File_Subsequent Treatment Data'.

A14. Please provide pdfs for the excluded studies listed in Table 6 and 7 of Appendix D related to ibrutinib in CLL regardless of line of treatment.

Table 11 and Table 12 list all the excluded studies from Table 6, Page 22 and Table 7, Page 43 of the CS Appendices, respectively, related to ibrutinib in CLL, with relevance to this question. The PDFs for each of these are provided in the supplementary reference pack within the zip folder '[A14] References'

Table 11: References excluded from the clinical SLR (Table 6, Page 22 of the CS Appendices), related to ibrutinib in CLL, with relevance to Question A14

No.	Database	Author	Publication year	Title	Journal	Volume	Issue	Pages	Exclusion reason
4	ProQuest	Naveed	2017	Analysis of Efficacy and Tolerability of Bruton Tyrosine Kinase Inhibitor Ibrutinib in Various B-cell Malignancies in the General Community: A Single-center Experience	Clinical lymphoma, myeloma & leukemia	17S		S53-S61	Population
12	ProQuest	Itchaki	2018	Experience with Ibrutinib for first-line use in patients with chronic lymphocytic leukemia.	Therapeutic advances in hematology	9	1	43178	Study design
13	ProQuest	Jain	2017	Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue Ibrutinib	Cancer	123	12	2268-2273	Outcomes
23	ProQuest	Aronson	2016	Ibrutinib increased survival more than chlorambucil in older patients with untreated chronic lymphocytic leukemia.	Annals of internal medicine	164	8	JC44	Study design
24	ProQuest	Lad	2018	Reduced Dose Ibrutinib Due to Financial Toxicity in CLL	Indian Journal of Hematology and Blood Transfusion				Population
30	ProQuest	Lipsky	2015	Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with Ibrutinib	Haematologica	100	12	1571-1578	Population
31	ProQuest	Maddocks	2015	Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia	JAMA oncology	1	1	80-87	Population
36	ProQuest	Mato	2017	Optimal sequencing of Ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients	Annals of oncology : official journal of the European Society for Medical Oncology	28	5	1050-1056	Population
37	ProQuest	Mato	2018	Toxicities and outcomes of 616 Ibrutinib-treated patients in the united states: A real-world analysis	Haematologica	103	5	874-879	Population

No.	Database	Author	Publication year	Title	Journal	Volume	Issue	Pages	Exclusion reason
50	ProQuest	Robak	2018	Single-agent Ibrutinib versus chemoimmunotherapy regimens for treatment-naïve patients with chronic lymphocytic leukemia: A cross-trial comparison of phase 3 studies.	American Journal of Hematology	93	11	1402-1410	Study design
65	ProQuest	Vela	2016	Ibrutinib for treatment of chronic lymphocytic leukemia.	American Journal of Health-System Pharmacy	73	6	367-375	Study design
79	ProQuest	Lad	2019	Reduced Dose Ibrutinib Due to Financial Toxicity in CLL	Indian Journal of Hematology and Blood Transfusion	35	2	260-264	Population
94	ProQuest	Chen	2018	A pilot study of lower doses of Ibrutinib in patients with chronic lymphocytic leukemia.	Blood	132	21	2249-2259	Population
98	ProQuest	Cuneo	2018	Efficacy of bendamustine and rituximab as first salvage treatment in chronic lymphocytic leukemia and indirect comparison with Ibrutinib: A GIMEMA, ERIC and UK CLL FORUM study	Haematologica	103	7	1209-1217	Population
104	ProQuest	Deeks	2017	Ibrutinib: A Review in Chronic Lymphocytic Leukaemia.	Drugs	77	2	225-236	Study design
136	CRD	NIHR HSC	2014	Ibrutinib (Imbruvica) for newly diagnosed chronic lymphocytic leukaemia – first line.	Birmingham: NIHR Horizon Scanning Centre (NIHR HSC)				Outcomes
150	CRD	IQWiG	2016	[Ibrutinib (chronic lymphocytic leukaemia): benefit assessment according to §35a Social Code Book V].	Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)				Study design
152	CRD	IQWiG	2016	[Ibrutinib (chronic lymphocytic leukaemia): Addendum to Commission A16-39].	Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)				Study design

Table 12: References from Table 7, Page 43 of the CS Appendices, related to ibrutinib in CLL, with relevance to Question A14

Citation
RCTs
• Barr, P. M. et al. Sustained efficacy and detailed clinical follow-up of first-line Ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica 103, 1502-1510, doi:10.3324/haematol.2018.192328 (2018). • Burger, J. A. et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 373, 2425-2437, doi:10.1056/NEJMoa1509388 (2015). • Burger, J. A et al. Ibrutinib for first-line treatment of older patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a 4-year experience from the RESONATE-2 study. European Hematology Society, PF343 (2018). • Burger, J. A. et al. Randomized trial of Ibrutinib vs Ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood 133, 1011-1019, doi:10.1182/blood-2018-10-879429 (2019). • Coutre, S. et al. Survival adjusting for crossover: phase 3 study of Ibrutinib vs. chlorambucil in older patients with untreated chronic lymphocytic leukemia/small lymphocytic lymphoma. Haematologica 103, e249-e251, doi:10.3324/haematol.2017.175380 (2018). • Michael Doubek, E. B., Martin Spacek, Lucile Baseggio, Renata Urbanova, Hervé Besson, Joris Diels, Jamie Garside, Nollaig Healy, Wafae Iraqi, Evelyne Callet-Bauchu, Lukas Smolej, Gilles Salles Single-agent Ibrutinib vs real world treatment for patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL): an adjusted comparison of RESONATE-2™ with the CLLEAR and LYON-SUD databases. European Hematology Society, E1024 (2017): • O'Brien, S. M. et al. Outcomes with Ibrutinib by line of therapy and post-Ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. American journal of hematology 94, 554-562, doi:10.1002/ajh.25436 (2019). • Shanafelt, T. D. et al. A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912). Blood 132, LBA-4, doi:10.1182/blood-2018-120779 (2018). • Tedeschi, A. et al. five-year follow-up of patients receiving Ibrutinib for first-line treatment of chronic lymphocytic leukemia: S107. HemaSphere 3, 5-6, doi:10.1097/01.HS9.0000558648.00957.de (2019). • Woyach, J. A. et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med 379, 2517-2528, doi:10.1056/NEJMoa1812836 (2018).
Non-RCTs
• Ahn, I. E. et al. Atypical Pneumocystis jirovecii pneumonia in previously untreated patients with CLL on single-agent Ibrutinib. Blood 128, 1940-1943, doi:10.1182/blood-2016-06-722991 (2016). • Ahn, I. E. et al. Depth and durability of response to Ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood 131, 2357-2366, doi:10.1182/blood-2017-12-820910 (2018). • Byrd, J. C. et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent Ibrutinib. Blood 125, 2497-2506, doi:10.1182/blood-2014-10-606038 (2015). • Byrd, J. C. et al. Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Blood 132, 3133, doi:10.1182/blood-2018-99-110847 (2018). • Coutre, S. E. et al. Extended Treatment with Single-Agent Ibrutinib at the 420 mg Dose Leads to Durable Responses in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Clin Cancer Res 23, 1149-1155, doi:10.1158/1078-0432.CCR-16-1431 (2017). • Dartigeas, C. et al. French Ibrutinib Observational Study (FIRE): real-world study of Ibrutinib treatment for chronic lymphocytic leukemia (CLL) in france: PF387. HemaSphere 3, 145-146,

doi:10.1097/01.HS9.0000559760.20946.1f (2019).
- Dimou, M. et al. Safety and efficacy analysis of long-term follow up real-world data with Ibrutinib monotherapy in 58 patients with CLL treated in a single-center in Greece. Leuk Lymphoma, 1-7, doi:10.1080/10428194.2019.1620944. (2019).
- Farooqui, M. Z. H. et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. The Lancet Oncology 16, 169-176, doi:10.1016/s1470-2045(14)71182-9 (2015).
- Mato, A. R. et al. Front-Line Ibrutinib Therapy for Chronic Lymphocytic Leukemia (CLL) in the Real World: Responses, Toxicity, Outcomes and Subsequent Therapies. Blood 130, 3011 (2017).
- Mato, A. R. et al. Outcomes of front-line Ibrutinib treated CLL patients excluded from landmark clinical trial. American journal of hematology 93, 1394-1401, doi:10.1002/ajh.25261 (2018).
- Mauro, F. R. et al. Ibrutinib and rituximab as front-line treatment for unfit patients with chronic lymphocytic leukemia (CLL). preliminary results from the GIMEMA LLC1114 study: PF375. HemaSphere 3, 139, doi:10.1097/01.HS9.0000559712.15168.1d (2019).
- O'Brien, S. et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. The Lancet. Oncology 15, 48-58, doi:10.1016/s1470-2045(13)70513-8 (2014).
- O'Brien, S. et al. Single-agent Ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood 131, 1910-1919, doi:10.1182/blood-2017-10-810044 (2018).
- Rhodes, J. et al. The Impact of Front-Line Ibrutinib Dose Reduction and Interruption on Outcomes in Chronic Lymphocytic Leukemia (CLL) Patients. Blood 130, 4313 (2017).
- Scalzulli, A. G., Giacomo Loseto, Giorgina Specchia, Anna Maria Giordano, Domenico Pastore, Giovanni Quintana, Patrizio Mazza, Alessandro Maggi, Nicola Di Renzo, Maria Rosaria De Paolis, Giuseppe Tarantini, Gaetano De Santis, Vincenzo Pavone, Antonino Greco, Maria Rosa Valvano and Nicola Cascavilla. Ibrutinib, Single Agent BTK Inhibitor, for Treatment Naïve (TN) and Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia: A Real-Life Experience from Rete Ematologica Pugliese (REP). Blood 132, 5557 (2018).

A15. Ibrutinib is unsuitable for patients with significant cardiac disease or patients receiving vitamin K antagonists. Would any of the patients in the del(17p)/TP53 mutation subgroup of CLL14 be considered unsuitable for ibrutinib therapy?

In the del (17p)/TP53 mutation subgroup of CLL14, 11 patients in the GClb arm and 20 patients in the VenG arm were on concomitant anticoagulants. Anticoagulants included warfarin, rivaroxaban and dabigatran

The cardiac conditions reported in patients with del(17p) and/or *TP53* mutation enrolled in CLL14 are listed in Table 13. As discussed on page 20 of the CS, ibrutinib is currently the standard of care in the del(17p)/*TP53* mutated subpopulation, however treatment options aside from ibrutinib are very limited and there is a high unmet need for patients who cannot tolerate ibrutinib, such as those with significant cardiac disease or bleeding risk. As a result of this, it is of key importance to broaden the therapeutic options for the del(17p)/*TP53* population to those with a different mechanism of action from the BCRis and to be able to treat patients with significant cardiac disease and bleeding risk.

Patient suitability for ibrutinib is a clinical decision. However, table 9 shows that these patients would be less likely to receive ibrutinib due to their cardiac risk factors.

Table 13: Cardiac disorders of patients with del(17p) and/or TP53 mutation enrolled in CLL14

Cardiac disorders	GCIb (n=24)	VenG (n=25)	Total (n=49)
Total number of subjects with at least one cardiac disorder in medical history	8 (33.3%)	11 (44.0%)	19 (38.8%)
Total number of cardiac disorders in medical history*	9 (37.5%)	15 (60%)	24 (49%)
Angina pectoris	1 (4.2%)	2 (8.0%)	3 (6.1%)
Arrhythmia	1 (4.2%)	1 (4.0%)	2 (4.1%)
Arteriosclerosis coronary artery	0	1 (4.0%)	1 (2.0%)
Atrial fibrillation	1 (4.2%)	2 (8.0%)	3 (6.1%)
Atrioventricular block complete	1 (4.2%)	0	1 (2.0%)
Atrioventricular block second degree	1 (4.2%)	0	1 (2.0%)
Cardiomyopathy	0	1 (4.0%)	1 (2.0%)
Cardiac failure congestive	1 (4.2%)	0	1 (2.0%)
Coronary artery disease	3 (12.5%)	1 (4.0%)	4 (8.2%)
Hypertensive heart disease	0	1 (4.0%)	1 (2.0%)
Myocardial ischaemia	0	3 (12.0%)	3 (6.1%)
Left ventricular hypertrophy	0	1 (4.0%)	1 (2.0%)
Supraventricular extrasystoles	0	1 (4.0%)	1 (2.0%)
Ventricular extrasystoles	0	1 (4.0%)	1 (2.0%)

* One subject may have more than 1 cardiac disorders in medical history

A16. Please provide an equivalent to Figure 6 but showing MRD negativity according to bone marrow.

Please note that bone marrow MRD by PCR was only assessed at Cycle 9 Day 1 and follow-up Month 3. This is presented in Table 14. No additional assessment beyond follow-up Month 3 is available.

Table 14: Undetectable MRD in bone marrow over time

Timepoint	Undetectable MRD ($<10^4$)	Detectable MRD	PD/Death	Withdrawn	Missing
VenG (N=216)					
C9D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GCIb (N=216)					
C9D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C7D1: Cycle 7, Day 1; C9D1: Cycle 9, Day 1; C12D1: Cycle 12, Day 1; FUM: follow-up month; GCIb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PD: progressive disease; VenG: venetoclax with obinutuzumab.

There was a general high concordance of MRD status between paired peripheral blood and bone marrow samples at EOT in both the GClb arm and VenG arm based on ASO-PCR analysis (see response to A17 and page 48 of CS). The strong concordance between MRD status in blood and bone marrow in matched samples suggests that the undetectable MRD rates in blood were comparable with undetectable MRD rates in bone marrow. Therefore, undetectable MRD in peripheral blood is a clear indication of undetectable MRD in VenG treated patients.

The high levels of undetectable MRD achieved in the VenG treated patients, particularly as measured in the bone marrow, indicates the depth of remission; patients achieving undetectable MRD levels are likely to have a long, treatment-free remission. In addition to the benefits received by patients, there are benefits to the healthcare system in the form of budget certainty and a delay to requiring the next line of treatment.

A17. Please provide a 2x2 table of agreement between bone marrow and peripheral blood for MRD negativity for each MRD assessment point, and one table combining all assessment points.

Tables of concordance between bone marrow and peripheral blood for undetectable MRD rates at the end-of-treatment assessment are presented in Table 15–Table 17 for GClb, VenG and the total population. Table 18–Table 20 present the same data, but also includes patients with missing samples in the detectable MRD group.

Table 15: Concordance between peripheral blood and bone marrow, measured by ASO-PCR at EOT assessment for GClb

GClb EOT assessment		Bone Marrow MRD		
		Undetectable MRD ($<10^4$)	Detectable MRD*	Total
Peripheral Blood MRD	Undetectable MRD ($<10^4$)	[redacted]	[redacted]	[redacted]
	Detectable MRD*	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Concordance Rate		[redacted]		

*Detectable MRD includes non-evaluable patients.
Abbreviations: EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease.

Table 16: Concordance between peripheral blood and bone marrow, measured by ASO-PCR at EOT assessment for VenG

VenG EOT assessment		Bone Marrow MRD		
		Undetectable MRD ($<10^4$)	Detectable MRD*	Total
Peripheral Blood MRD	Undetectable MRD ($<10^4$)	[redacted]	[redacted]	[redacted]
	Detectable MRD*	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Concordance Rate		[redacted]		

*Detectable MRD includes non-evaluable patients.
Abbreviations: EOT: end-of-treatment; MRD: minimal residual disease; VenG: venetoclax with obinutuzumab.

Table 17: Concordance between peripheral blood and bone marrow, measured by ASO-PCR at EOT assessment for all patients

All patients EOT assessment		Bone Marrow MRD		
		Undetectable MRD ($<10^4$)	Detectable MRD*	Total
Peripheral Blood MRD	Undetectable MRD ($<10^4$)	[redacted]	[redacted]	[redacted]
	Detectable MRD*	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Concordance Rate		[redacted]		

*Detectable MRD includes non-evaluable patients.
Abbreviations: EOT: end-of-treatment; MRD: minimal residual disease.

Table 18: Concordance between peripheral blood and bone marrow, measured by ASO-PCR at EOT assessment for GClb (including missing patients)

GClb EOT assessment		Bone Marrow MRD		
		Undetectable MRD ($<10^4$)	Detectable MRD*	Total
Peripheral Blood MRD	Undetectable MRD ($<10^4$)	[redacted]	[redacted]	[redacted]
	Detectable MRD*	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Concordance Rate		[redacted]		

*Detectable MRD includes non-evaluable and missing patients.
Abbreviations: EOT: end-of-treatment; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease.

Table 19: Concordance between peripheral blood and bone marrow, measured by ASO-PCR at EOT assessment for VenG (including missing patients)

VenG EOT assessment		Bone Marrow MRD		
		Undetectable MRD ($<10^4$)	Detectable MRD*	Total
Peripheral Blood MRD	Undetectable MRD ($<10^4$)	[redacted]	[redacted]	[redacted]
	Detectable MRD*	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]
Concordance Rate		[redacted]		

*Detectable MRD includes non-evaluable and missing patients.
Abbreviations: EOT: end-of-treatment; MRD: minimal residual disease; VenG: venetoclax with obinutuzumab.

Table 20: Concordance between peripheral blood and bone marrow, measured by ASO-PCR at EOT assessment for all patients (including missing patients)

All patients EOT assessment		Bone Marrow MRD		
		Undetectable MRD ($<10^4$)	Detectable MRD*	Total
Peripheral Blood MRD	Undetectable MRD ($<10^4$)	[redacted]	[redacted]	[redacted]
	Detectable MRD*	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]

Concordance Rate	[redacted]

*Detectable MRD includes non-evaluable and missing patients.
Abbreviations: EOT: end-of-treatment; MRD: minimal residual disease.

A18. Table 5 suggests MRD response rate was used in the economic model. If this is true, please explain how it is incorporated. It also suggests that overall survival was not used in the economic model. Please confirm.

We confirm that the economic model only makes use of the following CLL14 trial data, as opposed to what is highlighted in Table 5 on Page 29 of CS Document B:

- Independent review committee (IRC)-assessed progression-free survival (PFS)
- Overall survival
- Adverse effects
- Time-to-next treatment
- Health-related quality of life (explored in a scenario)

A19. The cut-off for adverse events included in Table 10 appears to be incorrect. Please confirm the criteria.

Table 10 on Page 39 of the CS Document B presents the details of the incidence of concurrent medical conditions at baseline in the CLL14 trial, rather than adverse events, as suggested.

Should this query refer to Table 10 as directed, please note that the two subheadings within the table were not in bold text.

- The first half of the table is for "Frequently reported concurrent conditions (>30% of patients overall)": the percentage difference applies to the specified categories of concurrent conditions, with the most frequent individual condition also being stated for "vascular disorders" and "metabolism and nutrition disorders". The second half of the table relates to "imbalanced concurrent conditions", irrespective of their overall frequency.

A20. Why was no attempt made to stratify patients based on the severity of their co-morbidities given the perceived impact on the observed overall survival?

The patients enrolled in the CLL14 study were stratified by Binet stage and by geographical location. These were the same stratification factors utilised in the CLL11 study.[4] As discussed in Question A1, most patients enrolled in CLL14, had comorbidities involving various organ classes which would complicate the stratification method given it is not an objective measure such as age or gender.

A21. Please comment on the possibility of patients receiving an additional course of VenG after completing or discontinuing their first course. Did this occur in CLL14? Could it happen in UK practice?

Overall during the CLL14 study, no patient received VenG beyond the planned 12 cycles as per protocol. Any additional treatment with VenG beyond the planned 12 cycles would be considered off-label use and not in line with the clinical trial design. The outcomes observed with VenG

demonstrated the ability to induce deep and durable responses in the form of a fixed-treatment duration.

Indirect and mixed treatment comparison

A22. Given the issues of a naïve comparison to the ibrutinib trials, please attempt a MAIC analysis to each of the four sources of ibrutinib data, using any available baseline characteristics.

For a MAIC analysis, matching variables are baseline patient or disease characteristics that have the potential to modify the treatment effect. NICE DSU guidance on 'Methods for population-adjusted indirect comparisons in submissions to NICE' suggests that the choice of variables to be matched/weighted on should be carefully considered.5 Including too many variables will reduce the effective sample size, negatively affecting the precision of the estimate; conversely, failure to include relevant variables will result in a biased estimate.

In this case, we encountered two issues that indirectly relate to the advice from DSU. Firstly, the CLL14 trial only includes 24 (as per original CS) patients in the VenG arm with the del(17p)/TP53 mutation, and therefore the effective sample size is very low. Second, the lack of available baseline characteristics in the comparator trial led to the conclusion that a MAIC is not feasible on the available evidence. An attempt to perform a MAIC would lead to inflated or unstable estimates of relative treatment effect as they depend heavily on just a small number of individuals and would be, in our opinion, not useful to inform the cost effectiveness model.

Moreover, it is not suggested practice to generalise baseline characteristics of specific subgroups to those of the whole trial population. This will lead to a significant amount of statistical bias with respect to matched characteristics. Combined with small sample sizes, we anticipate that results from suggested matched and adjusted analyses will not be more informative than those of the naïve comparison, presented in the original submission.

A23. Please perform a naïve indirect comparison to the ALLIANCE study.

The publication of Woyach et al. reporting on the Alliance trial includes a Kaplan-Meier curve for PFS in del(17p) subgroup, but not for OS.[6] After digitisation of the Kaplan-Meier curve of PFS and simulation of the patient level data, we performed a naïve Cox regression analysis.

Table 21 shows the results for PFS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation, using data from the Woyach et al. publication.[6] In Figure 10, the unadjusted hazard ratio (HR) and the 95% confidence intervals (CIs) are presented visually. The HR of [redacted] (95% CI: [redacted]) suggests ibrutinib has [redacted] PFS compared to VenG. However, there is [redacted] with respect to the treatment effect (log rank test: p=[redacted]).

Table 21: Unadjusted hazard ratio of PFS for Ibrutinib versus VenG, using the Woyach et al. publication

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value	Sample size
VenG (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 10: Unadjusted hazard ratio for PFS of ibrutinib versus VenG, using the Woyach et al. publication

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Results from the suggested analysis are aligned with those submitted as part of the original submission and are largely driven by a lack of statistical validity and small sample sizes, common issues seen in other NICE appraisals evaluating the cost-effectiveness of del(17p)/*TP53* mutation patients.[7] Since ALLIANCE is the study with the smallest sample size, we suggest that this is eventually disregarded, as originally suggested in CS Document B, Section B.2.9.2.

A24. Please perform a naïve indirect comparison to a set of IPD featuring a combination of all four ibrutinib studies.

Since Ahn et al.[8] and Farooqui et al.[9] report on the same clinical trial, to prevent double-counting, we considered Ahn et al. only for this analysis since this source provided KM data that could be utilised and is the most recent source of evidence. We have merged the PFS patient level datasets of Ahn et al.,[8] Mato et al.[10] and Woyach et al.,[6] and analysed this data compared to the CLL14 dataset.

Table 22 presents the results for PFS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation, using the combined data from the Ahn et al., Mato et al. and Woyach et al. publications. In Figure 11, the unadjusted HR and the 95% CIs are presented visually. The HR of [redacted] (95% CI: [redacted]) suggests ibrutinib has [redacted] PFS compared with VenG. However, there is [redacted] with respect to the treatment effect (log rank test: p=[redacted]).

Table 22: Unadjusted hazard ratio of PFS for ibrutinib versus VenG, using the combined population of the Ahn et al., Mato et al. and Woyach et al. publications

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value	Sample size
VenG (reference)					24
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	151

Abbreviations: PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 11: Unadjusted hazard ratio of PFS for ibrutinib versus VenG, using the combined population of the Ahn et al., Mato et al. and Woyach et al. publications

[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Since Woyach et al. did not report on OS, the combination of Ahn et al. and Mato et al. only was used for the OS analysis.

Table 23 shows the results for OS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation, using data from the Ahn et al. and Mato et al. publications. In Figure 12, the unadjusted HR and the 95% Cis are presented visually. The HR of [redacted] (95% CI: [redacted] suggests ibrutinib has superior OS compared to VenG. However, there is no statistical difference with respect to the treatment effect (log rank test: p=[redacted]).

Table 23: Unadjusted hazard ratio of OS for ibrutinib versus VenG, using the combined population of the Ahn et al. and Mato et al. publications

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value	Sample size
VenG (reference)					24
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	137

Abbreviations: PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 12: Unadjusted hazard ratio of OS for ibrutinib versus VenG, using the combined population of the Ahn et al. and Mato et al. publications

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

In addition, to align the results between PFS and OS, the combination of Ahn et al. and Mato et al. only for the PFS analysis has also been analysed.

Table 24 shows the results for PFS comparing ibrutinib versus VenG in previously untreated CLL patients with del(17p)/*TP53* mutation, using data from the Ahn et al. and Mato et al. publications. In Figure 13, the unadjusted HR and the 95% CIs are presented visually. The HR of [redacted] (95% CI: [redacted]) suggests ibrutinib has superior PFS compared with VenG. However, there is no statistical difference with respect to the treatment effect (log rank test: p=[redacted]).

Table 24: Unadjusted hazard ratio of PFS for ibrutinib versus VenG, using the combined population of the Ahn et al. and Mato et al. publications

Treatment	Unadjusted HR	CI 2.5%	CI 97.5%	p value	Sample size
VenG (reference)					24
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	142

Abbreviations: PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 13: Unadjusted hazard ratio of PFS for ibrutinib versus VenG, using the combined population of the Ahn et al. and Mato et al. publications

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

AbbVie do not consider that results from these analyses should be considered further since they suffer from a significant amount of bias and lead to similar conclusions to the analyses already submitted as part of the original CS Document B, Section B.2.9.

A25. The Mato and Ahn publications do not provide baseline characteristics for the del(17p) subgroup. The Mato study also contains 8 patients with TP53 mutation without del(17p) that are not included in the subgroup but are relevant to this appraisal. Did the company contact the authors of the Mato and Ahn studies to request baseline characteristics of the subgroup or individual patient data of all relevant participants?

Unsuccessful attempts were made to gather information by contacting the authors of these publications. For the analyses including the Mato et al. publication, we used the reported Kaplan–Meier curve of del(17p) only. There was no Kaplan-Meier curve available reporting on both patients with the del(17p) and *TP53* mutation, therefore the additional 8 patients with the *TP53* mutation were not included in the analyses.

It is worth highlighting that even with information on baseline characteristics from these publications, outcomes from a MAIC would not have been a reliable source of evidence, since the problem of having a small sample size would still be an area of concern and bias. Access to baseline characteristics of the patients with del(17p)/*TP53* mutations would not have led to a feasible MAIC analyses, since the CLL14 sample size would still be 24 patients.

A26. Please clarify the sample sizes used in the indirect comparison with Ahn described in Appendix D.1.4. It is stated sample size was reduced to 18 for the ibrutinib arm; please explain how this was derived?

Unfortunately, the reported sample size of 18 is incorrect. The correct sample size of the Ahn et al. data source is 34 The sample sizes used in the naïve indirect comparisons with Ahn et al. and also Mato et al. and Woyach et al. are provided in Table 25.

Table 25: Sample sizes used in the naïve indirect comparisons between VenG and ibrutinib in the del(17p)/*TP53* mutation population

Naïve comparison	Included population	CLL14 sample size (VenG)	Ibrutinib source sample size
Ahn et al.	*TP53*	24	OS and PFS: 34
Mato et al.	del(17p)	24	OS: 103 PFS: 108
Woyach et al.	del(17p)	24	OS: N/R PFS: 9

Abbreviations: N/R: not reported; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

A27. It is stated in in B.2.9.3 that the CLL14 trial only included patients aged ≥65 years, however Table 25 shows 25% of the (del)17p/P 53 mutation subgroup were aged <65 years. Please explain this and clarify the sample sizes used in the indirect comparison with Mato described in B.2.9.3.

It is indeed incorrect that the CLL14 trial only includes patients aged ≥65 years, but rather includes patients who are mostly aged ≥65 years (83.1% of the trial population were aged ≥65 years).

The sample sizes of the Mato data source, used in the naïve indirect comparison, are given for PFS and OS in Table 25 in Question A26.

Clinical effectiveness search

A28. In Appendix D, Table 7, p43: Studies included in the initial clinical SLR, but not of relevance to this decision problem or submission - lists 150 studies, but this also includes the 8 studies used for the indirect or mixed treatment comparisons listed in D1.2, Table 8, p52. Should these 8 studies be removed from Table 7?

Table 7 on Page 43 of the CS Appendices incorrectly lists all the studies identified in the initial clinical SLR, whether relevant to the submission or not, instead of only presenting those that were not of any relevance to this submission. Table 8 on Page 52 then separately presents those that were of relevance. As such, the eight publications listed in Table 8 should not also be present in Table 7.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY: Please provide utility scores calculated from EQ-5D-3L data collected in the CLL14 trial

Table 26 presents the details requested. Please note that the low number of responses in post-progression leads to a high degree of uncertainty in the utility estimates for the post-progression health state.

Table 26: EQ-5D utility values from CLL14 trial

EQ-5D scores in CLL14	With del(17p)/*TP53*		Without del(17p)/*TP53*	
	VenG (n=17)	GClb (n=14)	VenG (n=191)	GClb (n=193)
Baseline				
Number of responses / patients that responded	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free				
Number of responses	[redacted]	[redacted]	[redacted]	[redacted]
Number of eligible patients to respond	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard error)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression				
Number of responses	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients that responded	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard error)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: European Quality of Life 5 Dimensions (3 Level Version); GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

As seen in Table 26, PRO data were not available for all CLL14 trial participants at all time points. More responses were gathered for the pre-progression health state since at the time of follow-up (August 2018), only a small number of patients had progressed.

Pre-progression values seem to be unrealistically high for the non-del(17p)/*TP53* mutation group, exceeding age-adjusted perfect health in the GClb group. In the del(17p)/*TP53* mutation subgroup, these are lower but prone to bias due to the small sample size.

Post-progression values are unrealistically high for the non-del(17p)/*TP53* mutation population and well exceed those of age-adjusted perfect health, therefore cannot be used to accurately

inform reimbursement decisions. In the del(17p)/*TP53* mutation population, progressed PRO responders account for around 12% of the total VenG trial population and roughly around 36% for the GClb arm, resulting in a large degree of uncertainty in the summarised values. Results in the GClb arm for the del(17p)/*TP53* mutation population are presented for transparency but these should be disregarded as irrelevant to this decision problem.

It must be noted that differences between arms are not statistically significant across populations since p-values of the treatment arm coefficient were consistently above 0.05 in all regression analyses of the CLL14 EQ-5D 3L data. For transparency, correlation coefficient information on those analyses are presented in Table 27, Table 28, Table 29 and Table 30 for all modelled populations and health states.

Table 27 Results from EQ-5D-3L utility estimation non-del(17p) patients (PFS)

	Coefficient	**SE**	**df**	**t statistics**	**p-value**
Intercept	1.0398140	0.0761400	377.28	13.657	<0.000000000000002***
Arm (VEN+G)	-0.0121168	0.0166451	374.55	-0.728	0.467098
Age	-0.0031899	0.0010395	377.15	-3.069	0.002307**
Gender (male)	0.0538150	0.0177465	376.33	3.032	0.002594**
Time	-0.0008086	0.0002164	5313.64	-3.737	0.000188***
Number of observations		5,640	Number of patients		384

Significance level: * 10%; ** 5%; *** 1%

Table 28 Results from EQ-5D-3L utility estimation non-del(17p) patients (PPS)

	Coefficient	**SE**	**df**	**t statistics**	**p-value**
Intercept	0.988520	0.220175	36.010	4.490	<0.0000706***
Arm (VEN+G)	0.093349	0.070242	16.828	1.329	0.20160
Age	-0.002020	0.003013	29.908	-0.670	0.50783
Gender (male)	0.171497	0.061419	28.871	2.792	0.00919**
Time	-0.006959	0.003940	52.997	-1.766	0.08312
Number of observations		58	Number of patients		31

Significance level: * 10%; ** 5%; *** 1%

Table 29 Results from EQ-5D-3L utility estimation del(17p) patients (PFS)

	Coefficient	SE	df	t statistics	p-value
Intercept	1.287079	0.247469	24.57	5.201	0.0000233***
Arm (VEN+G)	-0.052957	0.063946	25.27	-0.828	0.4153
Age	-0.007255	0.003240	24.42	-2.239	0.0345*
Gender (male)	0.034706	0.063789	25.84	0.544	0.5911
Number of observations		356	Number of patients		29

Significance level: * 10%; ** 5%; *** 1%

Table 30 Results from EQ-5D-3L utility estimation del(17p) patients (PPS)

	Coefficient	SE	df	t statistics	p-value
Intercept	0.6048906	0.6301470	6.000	0.960	0.3742
Arm (VEN+G)	-0.3700338	0.1375809	6.000	-2.690	0.0361*
Age	-0.0005781	0.0095472	6.000	0.061	0.09537
Gender (male)	0.2865562	0.1354218	6.000	2.116	0.0787
Number of observations		10	Number of patients		7

Significance level: * 10%; ** 5%; *** 1%

In summary, although it would have been AbbVie's preference to use EQ-5D values for CLL14, we do appreciate that these are not in line with values commonly reported for CLL therapies and what has been previously accepted by NICE. Reported values from CLL14 lead to unrealistically high benefit for the group with most responses (non-del(17p)/*TP53* mutation) and also cannot be considered robust due to small sample size for the del(17p)/*TP53* mutation group. Therefore, we would ask that TA343 values are used instead, the new suggested base case from Question B2.

B2. Please explain the rationale for the use of the same utility values for all treatment arms

As stated in Table 48 on Page 120 and Table 64 on Page 131 of CS Document B, the same utility values for all treatment arms were applied as a conservative but simplifying approach using data from TA343 that best reflect this decision problem. Nonetheless, given the available evidence, we suggest that a more pragmatic breakdown of utilities is applied in the model's PFS health state. Specifically, we would suggest that the new base case incorporates the utility data presented in Table 31. Please refer to the general comment on page 7 of this response for a summary of the new base case we are submitting as part of this response document.

Table 31: New suggested base case utilities

Progression stage	Utility value	Source	Rationale for change/use
Pre-progression IV	0.670	TA343: PFS under IV treatment	VenG and GClb include IV treatment. This is applied for the fixed treatment duration of 12 months in the PFS state.
Pre-progression off treatment	0.820	TA343 Progression-free survival after initial treatment is completed (0.82)	VenG and GClb should not be taking into account IV disutility for the complete time on PFS health state. A value higher than that of pre-progression oral treatment (0.71) treatment but lower than that of perfect health is a more suitable option.
Pre-progression oral treatment	0.710	TA343 for Progression-free survival under oral treatment	A utility value reflective of oral treatment should be applied for the Ibrutinib arm PFS state.
Post-progression	0.600	TA343*: weighted average of the following utilities (progression after first-line treatment, PFS ± second-line treatment, relapsed line of treatment)	Used as base case and aligned with what has been accepted in previous NICE CLL appraisals.[1, 7]

Abbreviations: CLL: chronic lymphocytic leukaemia; GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

We believe that the new suggested base case is a more pragmatic reflection of the pre-progression health state and is aligned with past NICE appraisals. Model outcomes are not expected to change at a level that will impact the cost-effectiveness trend seen in any of the explored scenarios.

B3. PRIORITY: Please provide results from sensitivity analyses where health state utility values for the 'progression-free' and 'post-progression' health states are treatment-specific values obtained from the CL114 trial.

A scenario has been run using the per arm 'progression free' and 'post-progression' utilities calculated from the CLL14 trial. Table 32 provides the values used to run the scenarios. As described in Question B1, the utility values from the CLL14 trial are unrealistically high, exceeding age-adjusted perfect health. Health economics experts at an HTA advisory board agreed with this conclusion.

Table 32: Progression-free and post-progression utilities from the CLL14 trial used in the new scenario analyses

Treatment arm	PFS (IV treatment)	PPS
With del(17p)/*TP53*		
VenG	[redacted]	[redacted]
GClb is not a comparator, no change made to ibrutinib arm		
Without del(17p)/*TP53*		
VenG	[redacted]	[redacted]
GClb	[redacted]	[redacted]

Abbreviations: GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

Table 33 presents the incremental discounted costs, incremental discounted QALYs, ICER, and net monetary benefit for both the 'with del(17p)/*TP53* mutation' group and the 'without del(17p)/*TP53* mutation' group for these new scenarios at LIST price.

Table 33: Cost-effectiveness results from the new scenario analyses at LIST price

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER (incremental cost per QALY)	Net monetary benefit
Scenario 1: with del(17p)/*TP53* VenG PFS (IV) = 0.745, PPS = 0.471				
Base case: with del(17p)/*TP53*	[redacted]	0.377	Dominant	[redacted]
Scenario 1: vs ibrutinib	[redacted]	0.409	Dominant	[redacted]
Scenario 2: without del(17p)/*TP53*, VenG PFS (IV and post IV*) = 0.829, PPS = 0.969 GClb PFS (IV and post-IV*) = 0.841, PPS = 0.876				
Base case: without del(17p)/*TP53*	[redacted]	1.148	Dominant	[redacted]
Scenario 2: vs GClb	[redacted]	-0.165	[redacted]	[redacted]

*Same utility also applied to post-IV since the literature post-IV utility value is less than the utility generated from the CLL14 trial while on IV.
**This is a South West Quadrant ICER. Positive net monetary benefit (NMB) values imply cost saving to the NHS

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life-year; VenG: venetoclax with obinutuzumab.

B4. In CS, page 118, it is stated that "*None of the identified health-related quality-of-life studies elicited utility values from a UK population using EQ-5D, and therefore were not in line with the NICE reference case*." Please clarify whether this statement would disqualify studies reporting EQ-5D HSUVs where health state description was derived from a non-UK population though health state valuation is based on the recommended UK-specific EQ-5D value set.

Table 30 on Page 175 of the CS Appendices summarises the health-related quality of life studies identified in the SLR and their consistency with the NICE reference case. Only three of the 16 identified publications (Kay et al. 2012,[11] Pashos et al. 2012,[12] and Pashos et al. 2013[13]) used the EQ-5D survey to measure health-related quality of life, however, the data were from populations based in the USA. All three publications report on the same study, Connect CLL®: the exact EQ-5D value set is not reported but is assumed to be US values, and hence the studies were considered to not be in line with the NICE reference case.

Although mean index values are given in Kay et al. 2012[11] and Pashos et al. 2013,[13] as AbbVie do not have access to the IPD from the registry study, it is not possible to value these data using the UK value set.

B5. Please clarify the reasons for not reporting additional sensitivity analyses using alternative EQ-5D HSUVs identified in the relevant literature and available in previous appraisals, especially in light of the NICE reference case requiring that when more than one plausible set of EQ-5D data is available in the literature, sensitivity analyses should be carried out to show the impact of the alternative utility values.

Table 34 presents a subset of all utilities per health state which are being included as part of additional sensitivity analyses. A complete list of all utilities extracted from the systematic literature review is also provided which can be found in Table 36. A 'Comment' column has been added to this complete list of utilities to justify why certain utilities were included or excluded as part of the sensitivity analyses.

Table 35 presents the incremental discounted costs, incremental discounted QALYs, ICER, and net monetary benefit for both the 'with del(17p)/*TP53* mutation' group and the 'without del(17p)/*TP53* mutation' group for these new scenarios.

Table 34: Overview of utility values being used in the scenarios

Author, year and region	Health state (modelled health state)	Utility value
Adena, M, 2014 [14] Australia	Progressed (PPS)	0.618
Chen, Q, 2016[15] USA	Relapsed (PPS)	0.68
Herring, W, 2016[16] Canada	Progressive disease and BSC (PPS: VenG and GClb arms)	0.75

Singh, M, 2017[17] Not reported	No active treatment (PFS after FTD: VenG and GClb arms) Disease progression after first-line Therapy (PPS)	0.89 0.66
Soini, E, 2016[18] Finland (Please note these values are similar but not identical to the Kosmos source)	PFS without IV treatment PFS with IV treatment PFS off treatment PD	0.672 0.634 0.776 0.563

Abbreviations: FTD: fixed treatment duration; IV: intravenous; PD: progressive disease; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

Table 35: Cost-effectiveness results from additional utilities scenario analyses (LIST price)

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER (incremental cost per QALY)	Net monetary benefit
With del(17p)/*TP53* mutation **Scenario 3: VenG and ibrutinib PPS = 0.618** **Scenario 4: VenG and ibrutinib PPS = 0.68** **Scenario 5: VenG and ibrutinib PPS = 0.75** **Scenario 6: VenG (after FTD) PFS = 0.89, VenG and ibrutinib PPS = 0.66** **Scenario 7: VenG PFS (IV) = 0.634, PFS (post FTD) = 0.776, ibrutinib = 0.672, PPS = 0.563**				
Base case: with del(17p)/*TP53*	[redacted]	0.377	Dominant	[redacted]
Scenario 3: vs ibrutinib	[redacted]	0.381	Dominant	[redacted]
Scenario 4: vs ibrutinib	[redacted]	0.395	Dominant	[redacted]
Scenario 5: vs ibrutinib	[redacted]	0.411	Dominant	[redacted]
Scenario 6: vs ibrutinib	[redacted]	0.632	Dominant	[redacted]
Scenario 7: vs ibrutinib	[redacted]	0.355	Dominant	[redacted]
Without del(17p)/*TP53* mutation **Scenario 8: VenG and GClb PPS = 0.618** **Scenario 9: VenG and GClb PPS = 0.68** **Scenario 10: VenG and GClb PPS = 0.75** **Scenario 11: VenG and GClb (after FTD) PFS = 0.89, VenG and GClb PPS = 0.66** **Scenario 12: VenG and GClb PFS (IV) = 0.634, PFS (Post FTD) = 0.776, PPS = 0.563**				
Base case: without del(17p)/*TP53*	[redacted]	1.148	Dominant	[redacted]
Scenario 8: Vs GClb	[redacted]	1.054	Dominant	[redacted]
Scenario 9:	[redacted]	0.730	Dominant	[redacted]

Vs GClb				
Scenario 10: Vs GClb	[redacted]	0.364	Dominant	[redacted]
Scenario 11: Vs GClb	[redacted]	1.200	Dominant	[redacted]
Scenario 12: Vs GClb	[redacted]	1.112	Dominant	[redacted]

Abbreviations: FTD: fixed treatment duration; ICER: incremental cost-effectiveness ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Table 36: List of utility values from studies picked up by the Economic evaluation and HRQoL SLRs

Author, year and region	Measurement and valuation of preference based outcomes	Health state utility scores	Source	Comments
Adena, M, 2014 Australia	EQ-5D values were extracted from the literature	Unprogressed: 0.805 ± 10% Progressed: 0.618 ± 10%	Wild D, Walker M, Pettengell R, et al., editors. Utility elicitation in patients with follicular lymphoma. 11th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); Philadelphia: Value Health; 2006.	PFS (Not treatment specific) Progressed: 0.618 ± 10%
Barnes, JI, 2018 USA	Utilities extracted from the literature	PFS on initial therapy - ibrutinib 0.71 PFS of initial therapy - comparator 0.67 PFS not on therapy after initial therapy 0.82	Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leuk Lymphoma. 2015;56(5):1320-1326.	Being used in the updated version of the model with treatment specific utility
Batty, AJ, 2010 UK	Not reported	Not reported	Not applicable	-
Becker, U, 2016 UK	Utilities extracted from the literature	PFS under oral treatment 0.71±0.20 PFS under IV treatment 0.67±0.22 PFS under IV treatment with increased hospital visits 0.55±0.26 PFS health state after treatment 0.82±0.17	Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leuk Lymphoma. 2015;56(5):1320-1326.	Being used in the updated version of the model with treatment specific utility
Bertwistle, D, 2013	Not reported	Not reported	Not applicable	-

Colombia				
Bertwistle, D, 2013 Mexico	Not reported	Not reported	Not applicable	-
Bosch, F, 2009 Spain	Not reported	Not reported	Not applicable	-
Cameron, H, 2014 Canada	Not reported	Not reported	Not applicable	-
Casado, LF, 2016[19] Spain	Utilities extracted from the literature	PFS under oral treatment (0.67:0.75) 0.71 PFS under IV treatment (0.63:0.71) 0.67 PFS under IV treatment with increased hospital visits (0.50:0.61) 0.55 PFS after treatment (0.78:0.85) 0.82	Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leuk Lymphoma. 2015;56(5):1320-1326.	Being used in the updated version of the model with treatment specific utility
Chen, Q, 2016 USA	Utilities extracted from the literature	Watch and wait 1.00 1L complete response (0.88:0.93) 0.91 1L partial response (0.81:0.87) 0.84 1L no response (0.75:0.82) 0.78 Relapsed (0.64:0.72) 0.68	Beusterien KM, Davies J, Leach M, et al: Population preference values for treatment outcomes in chronic lymphocytic leukaemia: A cross-sectional utility study. Health Qual Life Outcomes 8:50, 2010 Marsh K, Xu P, Orfanos P, et al: Model-based cost-effectiveness analyses for the treatment of chronic lymphocytic leukaemia: A review of methods to model disease outcomes and estimate utility.	Other utilities not treatment specific. Relapsed 0.68 (0.64:0.72)

			Pharmacoeconomics 32:981-993, 2014	
Chiattone, C, 2010 Brazil	Not reported	Not reported	Not applicable	-
Dervaux, B, 2007 France	Not reported	Not reported	Not applicable	-
Herring, W, 2016 Canada	EQ-5D values were extracted from the COMPLEMENT-1 trial	Stable disease 0.76 Partial response 0.79 Complete response 0.78 Progressive disease and BSC 0.75	COMPLEMENT-1	Other utilities not treatment specific / relevant to the model. Progressive disease and BSC 0.75 (Can be used for GClb and VEN+G arms PPS) Should not be assessed for Ibrutinib since PFS (Oral treatment) = 0.71 which would be < PPS
Holtzer-Goor, K, 2012 Netherlands	Not reported	Not reported	Not applicable	-
Hornberger, JC, 2010 USA	Not reported	Not reported	Not applicable	-
Hornberger, J, 2012 USA	Not reported	Not reported	Not applicable	-
Kapedanovska Nestorovska, A, 2017 Macedonia	Not reported	Not reported	Not applicable	-

Kawalec, P, 2009 Poland	Not reported	Not reported	Not applicable	-
Kongnakorn, TE, 2014 USA	Utilities were derived from published literature	Patients on treatment 1L 0.74 Patients who responded to treatment 0.80 Patients who progressed 0.60	Walker S, Palmer S, Erhorn S, et al. Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia. Health Technol Assess. 2009;13(13 Suppl 1):35–40.	Other utilities not treatment specific / relevant to the model. Utility are not treatment specific and PPS utility is already being used
Kousoulakou H, 2017 Greece	Not reported	Not reported	Not applicable	-
Lupu, A, 2010 Romania	Not reported	Not reported	Not applicable	-
Malin, J, 2010 USA	Not reported	Not reported	Not applicable	-
Mandrik, O, 2015 Ukraine	Not reported	Not reported	Not applicable	-
Müller, D, 2016 Germany	Not reported	Not reported	Not applicable	-
Paquete, AT, 2017 Portugal	Utilities extracted from the literature	PFS under oral treatment 0.71 PFS under IV treatment 0.67 PFS under IV treatment with increased hospital visits 0.55 PFS after treatment 0.82	Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leuk Lymphoma. 2015;56(5):1320-1326.	Being used in the updated version of the model with treatment specific utility
Pearson, IV, 2015 UK	Not reported	Not reported	Not applicable	-
Pompen, M, 2009 Netherlands	Not reported	Not reported	Not applicable	-

Reyes, C, 2014 USA	Not reported	Not reported	Not applicable	-
Reyes, C, 2014 USA	Not reported	Not reported	Not applicable	-
Roussel, M, 2009 France	Not reported	Not reported	Not applicable	-
Saenz, A, 2016 Colombia	Not reported	Not reported	Not applicable	-
Singh, M, 2017 Not reported	Utilities were derived from the published literature, based on standard gamble, EQ-5D, time trade-off and EORTC.	From Beusterien et al, 2010: CR: complete absence of symptoms 0.91±0.11 PR: >50% reduction in symptoms 0.84±0.14 No change in symptoms 0.78±0.14 Progressive disease 0.68±0.20 2nd line treatment 0.71±0.17 3rd line treatment 0.65±0.22 From Holtzer-Goor, 2015: All patients 0.85±0.10 Norm score 0.89±0.00 No active treatment 0.89±0.10 On-treatment with chlorambucil monotherapy 0.82±0.20 Other patients 0.85±0.20 From Kosmas et al, 2015 and Shingler et al: PFS without therapy 0.82 PFS on initial oral therapy 0.71 PFS on initial intravenous therapy 0.67 PFS on initial therapy with increased hospital visits 0.55 Disease progression after 1L	Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, Bramham-Jones S Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010;8:50. Epub 2010/05/21. Holtzer-Goor KM, Schaafsma MR, Joosten P, Posthuma EF, Wittebol S, Huijgens PC, Mattijssen EJ, Vreugdenhil G, Visser H, Peters WG, Erjavec Z, Wijermans PW, Daenen SM, van der Hem KG, van Oers MH, Uyl-de Groot CA. Quality of life of patients with chronic lymphocytic leukaemia in the Netherlands: results of a longitudinal multicentre study. Qual Life Res.	Other utilities not treatment specific / relevant to the model. Chen, Q, 2016 USA (PPS = 0.68 already included in utility scenario list) From Holtzer-Goor, 2015: No active treatment 0.89±0.10 Kosmos - Being used in the updated version of the model with

		therapy 0.66 PFS without second-line therapy 0.71 Further progression 0.59 PFS on second-line therapy 0.55 Relapsed lines of treatment 0.42 From Kay et al, 2015: Baseline before 1L therapy 0.87±0.14 Baseline before 2L therapy 0.84±0.15 Baseline before higher line therapy 0.83±0.15 From Woods et al, 2012: On treatment 1L 0.7±0.11 From Herring et al (COMPLEMENT-1): Baseline 0.75 CR 0.78 PR 0.79 Stable disease 0.76 PD/BSC 0.75 From Hancock and Hyde, 2002: PFS 0.8 PD 0.6	2015;24:2895-906. Epub 2015/07/25. Kosmas CE, Shingler SL, Samanta K, Wiesner C, Moss PA, Becker U, Lloyd AJ. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leukemia & lymphoma. 2015;56:1320-6. Epub 2014/09/13. Shingler SL, Kosmas CE, Samanta K, Wiesner C, Lloyd AJ. Health State Utilities for Chronic Lymphocytic Leukemia. Value in Health.17:A92 Kay NE, Flowers CR, Weiss M, Lamanna N, Flinn IW, Grinblatt D, Kipps TJ, Kozloff M, Lerner S Sharman J, Yu R, Khan ZM, Street TK, Swern AS, Sullivan KA, Pashos CL. Variation in Health-Related Quality of Life by Line of Therapy of Patients with Chronic Lymphocytic Leukemia. Blood. 2015;120:3926. Woods B, Hawkins N, Dunlop W, O'Toole A,	treatment specific utility From Kosmas et al, 2015 and Shingler et al: Disease progression after 1L Therapy: 0.66

			Bramham-Jones S. Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: a cost-utility analysis. Value Health. 2012;15:759-70. Epub 2012/08/08. Herring W, Pearson I, Purser M, Nakhaipour HR, Haiderali A, Wolowacz S, Jayasundara K. Cost-Effectiveness of Ofatumumab Plus Chlorambucil in First Line Chronic Lymphocytic Leukemia in Canada. Value in Health.17:A634 Hancock S WB, Hyde C,. Fludarabine as first line therapy for chronic lymphocytic leukaemia. Report 42. UK: Department of Public Health & Epidemiology, University of Birmingham 2002.	From Herring et al (COMPLEMENT-1): PD/BSC Already included in scenario list From Hancock and Hyde, 2002: PD same value being used in
Singh, M, 2017 Not reported	Not reported	Not reported	Not applicable	-
Sinha, R, 2018 UK	Utilities extracted from the literature	PFS under oral treatment 0.71±0.20 PFS under IV treatment 0.67±0.22 PFS under IV treatment with increased hospital visits 0.55±0.26 PFS health state after treatment 0.82±0.17	Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival.	Kosmos - Being used in the updated version of the model with treatment specific utility

			Leuk Lymphoma. 2015;56(5):1320-1326.	
Smet, A, 2017 Belgium	Not reported	Not reported	Not applicable	-
Soini, E, 2016 Finland	Utilities extracted from the literature	PFS without IV treatment 0.672±0.189 PFS with IV treatment 0.634±0.208 PFS with increased hospital visits 0.520±0.246 PFS off treatment 0.776±0.181 PD 0.563	Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression-free survival. Leuk Lymphoma. 2015;56(5):1320-1326.	PFS without IV treatment 0.672±0.189 PFS with IV treatment 0.634±0.208 PFS off treatment 0.776±0.181 PD 0.563
Vandekerckhove, S, 2012 Netherlands	Not reported	Not reported	Not applicable	-
Leroy Veenstra, D, 2014 UK	Not reported	Not reported	Not applicable	-
Walzer, S, 2013 UK	Not reported	Not reported	Not applicable	-
Woods, B, 2012 England and Wales	Utilities were derived from the literature	Baseline utility 0.70±0.22 CR 0.91±0.11 PR 0.84±0.14 No change 0.78±0.14 PD 0.68±0.20 No change + 1-2 nausea 0.73±0.17 No change + 1-2 nausea/vomiting 0.73±0.16 No change + 1-2 diarrhoea 0.70±0.19 No change + 3-4 anaemia 0.69±0.18 No change + 3-4 pyrexia 0.67±0.17 No change + 3-4 pneumonia 0.58±0.19	Knauf WU, Lissichkov T, Aldaoud A, et al. Bendamustine induces higher remission rates, prolongs progression free survival as well as time to next treatment, and improves overall survival for patients in complete remission without compromising quality of life when compared to chlorambucil in first line	Other utilities not treatment specific / relevant to the model. PD same as Chen, Q, 2016 USA

		No change + second-line treatment 0.71±0.17	treatment of chronic lymphocytic leukaemia. Blood (ASH annual meeting abstracts) 2010; 116:2449. Versteegh MM, Rowen D, Brazier JE, Stolk EA. Mapping onto EQ-5D for patients in poor health. Health Qual Life Outcomes 2010;8:141.	
Yagudina, R, 2015 Russia	Not reported	Not reported	Not applicable	-

B6. PRIORITY: We notice an unsupported assumption in the company's economic model regarding the application of costs of later lines of therapy. For example, in the non del17p/TP53 mutation population, the average time on next treatment is 7.13 years for the GCIb arm throughout which the costs of the second line therapies (ibrutinib and Ven+R) are applied. However, the average times on ibrutinib and Ven+R are 3.25 and 2.03 years respectively (as reported in the external studies provided by the company). Please provide evidence to support the application of the costs of the later lines of therapy for such an extended duration.

Experts have confirmed that older CLL patients with comorbidities are not expected to exceed more than three lines of treatment in total with commonly used agents being VenR and ibrutinib in treatment experienced R/R CLL patients. Each of these lines are given for 2 and 3–5 years respectively and not consecutively but with a break between lines of therapy. These variables, as explained below, could not be accurately calculated therefore the fairest, although not entirely accurate, way of modelling for both arms would be continuously until end-of-life (EOL) treatment is given.

There is no evidence available in the literature specific to R/R CLL patients with comorbidities. The limited published literature is on a blend of fit and unfit R/R patients and it is expected that survival outcomes will be impacted by fitness for chemotherapy. Moreover, there is no published literature or established guidelines on the period from progression to initiation of next line of therapy therefore this variable could not be reliably calculated as an average and in real life is decided on a case by case basis according to UK clinicians.

Therefore, it would not have been feasible to calculate a treatment sequencing model to best reflect duration and lines of therapy at R/R CLL setting. Given the lack of published evidence and real-life data on use of R/R agents on CLL patients with comorbidities, it was decided that the fairest approach to calculate this would be for both arms continuously using a basket of costs until EOL care costs kick-in. The duration for which costs at R/R setting occur per arm is outcome-driven using the difference in extrapolations from time-to-next treatment (TTNT) and OS curves from CLL14. The average time on subsequent treatments is largely driven by the long-term extrapolations and can be justified by time spent in these health states per arm.

Specifically, in order to calculate the number of patients who receive the next line of treatment, for the VenG and GCIb treatment arms the difference between overall survival and time to next treatment is used per cycle. In order to calculate the per cycle cost each patient receives, a weighted average of the basket of subsequent treatments (i.e., VenR, ibrutinib, or venetoclax monotherapy) are assumed based on clinician opinion (50:50). The per cycle cost is calculated by assuming the length of treatment while on 2nd line treatment. A median time on second line treatment was included based on literature values so the model could calculate an accurate average cost per cycle which could be applied to patients who had progressed and remained alive in every cycle. Please note that VEN+R is given for a fixed treatment duration and based on literature this value was 24.4 months, so it is unlikely that the mean time on subsequent treatment with VEN+R would differ substantially from the 24 months. However, for ibrutinib and venetoclax monotherapy, the mean time on subsequent treatment may vary since these are treat to progression therapies. More detail on the rationale and method of obtaining this mean duration of treatment is further clarified in our response to Question B11.

In conclusion, a pragmatic approach to estimating post-progression treatment costs per cycle, which does not favour either treatment arm, was selected. The key driver of post-progression costs is thus the time spent between initiation of 2L treatment and death (in PPS health state), which is outcome driven: the CLL14 trial demonstrated that VenG patients had superior PFS compared to GClb and therefore took longer to initiate next line of treatment as per the TTNT curves from CLL14. As described in the response to A16 and validated by UK experts, this can be explained by higher uMRD rates compared to GClb, which is indicative of longer remissions before requiring the next line of treatment.

B7. Please clarify the rationale for using the same standard error of 10% (or any other value) uniformly across a range of diverse parameters including resource use, probability of events, unit costs and HSUVs.

This submission followed the approach previously accepted by NICE for CLL in TA561.[2] However, in response to this question we have reverted to the original sources and identified standard errors where possible, either by using the sample size or using the published standard errors. Standard errors were identified for four disutility values which have now been added to the updated version of the model in the 'Utilities' sheet and the 'Input' sheet. Table 37 provides an overview of all the inputs and steps taken per input to calculate a standard error.

Table 37: Overview of model inputs and their respective standard error calculated

'Model sheet name' : Model inputs	Method of standard error applied	Changes applied in new model version
'Main board' : Patient characteristic: Used in the model:	Standard error calculated using CLL14 sample size	No change
'Survival' : Comparator efficacy	95% confidence interval or standard error calculated from the trial data or NMA	No change
'Resource use': Resource use per health state:	Input has been elicited from clinical experts therefore standard error calculation was not possible	No change
'Costs': 1. Costs per administration (IV / Rapid IV / SC) 2. Resource use activity costs 3.Terminal care 4.Mean time on subsequent treatment	1 + 2: Inputs were calculated from NHS reference costs which did not provide standard errors 3. Terminal care costs were calculated by inflated costs provided in Round et al 2015. Round et al 2015 only provided a mean value for terminal care. 4. Standard errors not provided	No change

'Utilities': Utilities	Kosmas et al. 2015 reported the mean utility values and their standard deviation (see next column), from a simple summary statistic; no sample size and SE are reported	PFS under oral treatment 0.71 (SD 0.20) PFS under IV treatment 0.67 (SD 0.22) PFS health state after treatment 0.82 (SD 0.17)
Disutilities	Lloyd et al 2006 and the HTA submissions which used the source did not provide a standard error or confidence interval Beusterien et al. 2010 and Tolley et al. 2013 include standard deviation values of the initial utility mean and the utility mean with the disutility for AE included; we then calculate the difference between the standard deviation of these two utility values and divide it by the sample size to obtain the SE) Nafees et al. 2008 reported the SE for neutropenia	Diarrhoea: SE = 0.005 Thrombocytopenia: SE = 0.012 Sepsis / pneumonia: SE = 0.0039 Neutropenia SE = 0.016
1. Adverse event probabilities 2. Adverse event costs	1. Standard error calculated using original source sample size 2. Inputs were calculated from NHS reference costs which did not provide standard errors	No change

Abbreviations: AE: adverse event; IV: intravenous; NHS: National Health Service; NMA: network meta-analysis; PFS: progression-free survival; SC: subcutaneous; SE: standard error.

B8. In CS, page 136, it is explained that "*In cases where uncertainty data was not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed."* In the economic model uncertainty (variability) around OS and PFS HR for Ibrutinib appears to be set to the assumed value of 10% of the mean (sheet "Inputs", cells B53:D53 and cells B55:D55). However, uncertainty values (standard errors) for the specific parameters have already been calculated and are reported in sheet "Survival", cells F47 and F52 for PFS and OS, respectively). Please explain this discrepancy and the choice of representing uncertainty around these estimates as 10% of the mean values.

The discrepancy described is a modelling issue and has now been updated in the new version of the model '*[B2] [B7] [B8] ID1402 (ACIC)_VenG_CLL_NICE Economic Model*,' which is being sent with the clarification questions response. The 'input' sheet in the model has now been updated so that standard error around the OS and PFS HR is being correctly applied.

B9. PRIORITY: Please clarify how uncertainty in the *distribution parameters* for OS, PFS, ToT and TTnT have been incorporated in the deterministic and

probabilistic sensitivity analyses, and how this is reflected in the reported results (including the probabilistic analysis outcomes, cost-effectiveness planes and cost-effectiveness acceptability curves).

Uncertainty in ToT is not assessed since all datapoints were observed directly in the CLL14 trial, and no extrapolation was required.

The deterministic analyses do not take account of individual parameter uncertainty within the survival distributions for OS, PFS, and TTNT. The reason for this is that the survival parameters are correlated and hence it would be incorrect to vary these parameters individually and the results would be uninterpretable.

The overall uncertainty surrounding the OS, PFS and TTNT survival curves is taken into account in the probabilistic sensitivity analysis, where the covariance across survival distribution parameters is taken into account during sampling (using Cholesky decomposition). The Cholesky decomposition matrices can be found in the 'Survival parameter' sheet.

The impact of fitting alternative parametric models was tested, which can be considered a form of structural sensitivity analysis. Extensive scenario analyses were conducted with alternative survival distributions using both independent and dependent models, as presented in CS.

B10. PRIORITY: In CS p.85, the company points out a discrepancy between the number of cycles of Clb used in the control arm of CLL14 (12 cycles) and the number of cycles of Clb used in UK clinical practice (six cycles). To reflect UK clinical practice more closely, please provide a revised version of the model where Clb is administered over six cycles in line with current NHS clinical practice.

Note that there is variability in the dose and number of cycles of Clb used in UK clinical practice, as shown in Table 38. The Christie NHS Foundation Trust, for example recommends up to 12 cycles of Clb at a dose higher than that used in the CLL14 trial.

Table 38: Dose and number of cycles of Clb used in UK clinical practice

Trust/Organisation	Recommended Dose	Link to local protocol
Thames Valley Strategic Clinical Network	Clb 0.5mg/kg, D1 and D15, 6 cycles	http://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-chemo-protocols/L-22-obinutuzumab-chlorambucil.pdf
South East London Cancer Network	Clb 10mg/m^2 Days 1 to 7, for up to 12 cycles	http://www.londoncanceralliance.nhs.uk/media/36488/CLL_chlorambucil_protocol__v2_0.pdf
The Christie NHS Foundation Trust	Clb 10mg/m^2 Days 1 to 7, for up to 12 cycles	https://gmcancerorguk.files.wordpress.com/2019/04/cll-guidelines_v4.0-feb-2019.pdf

Northern Cancer Alliance	Clb 10mg/m^2 Days 1 to 7, for up to 12 cycles	http://www.northerncanceralliance.nhs.uk/wp-content/uploads/2019/01/Haematology-Cancer-Clinical-Guidelines-S9-CLL-Lymphoprolifera-Disorders.pdf
University Hospital Southampton NHS Foundation Trust	Clb 0.5mg/kg, D1 and D15, 6 cycles or Clb 10 mg D1-D14, 6 cycles	https://www.uhs.nhs.uk/Media/SUHTExtranet/Services/Chemotherapy-SOPs/CLL/Chlorambucil-2-Obinutuzumab.pdf https://www.uhs.nhs.uk/Media/SUHTExtranet/Services/Chemotherapy-SOPs/CLL/Chlorambucil-14-Obinutuzumab.pdf
South West Clinical Network	Clb 0.5mg/kg, D1 and D15, 6 cycles	https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2018/11/obinutuzumab-protocol.pdf

Since UK practice and guidelines on dose, number of cycles and days of administration vary, multiple versions of the ERG request have been provided for transparency:

- [B10] ID1402 (ACIC)_VenG_CLL_NICE Economic Model_Clb_6Cy_0.5mg
- [B10] ID1402 (ACIC)_VenG_CLL_NICE Economic Model_Clb_6Cy_10mg_D1,15
- [B10] ID1402 (ACIC)_VenG_CLL_NICE Economic Model_Clb_6Cy_10mg_D1,15

The results are summarised in Table 39. Note that all the scenarios presented use a conservative cost calculation based on 6 cycles of Clb (as requested by the ERG), even though some UK centres do use 12 cycles of Clb. Furthermore, these scenarios make an unjustified assumption of a full 12-cycle efficacy benefit of Clb as per the CLL14 trial outcomes as opposed to only a 6-cycle efficacy benefit of Clb which would be expected in these scenarios. Nevertheless, even with this unjustified assumption on efficacy, VenG remains dominant in the non-del(17p)/*TP53* mutation population.

Table 39: Economic model results for the scenario where GClb cost is aligned to UK clinical practice (efficacy remains as per CLL14)

Incremental results of VenG vs GClb	Incremental discounted costs	Incremental discounted QALYs	ICUR (incremental cost per QALY)	Net monetary benefit
Base case	[redacted]	1.148	Dominant	[redacted]
Scenario 1: Clb 6 cycles (D1,15) 0.5mg/kg (bodyweight)	[redacted]	1.148	Dominant	[redacted]
Scenario 2: Clb 6 cycles (D1,15) 10mg/m2 (body surface area)	[redacted]	1.148	Dominant	[redacted]
Scenario 3: Clb 6 cycles (D1-7)	[redacted]	1.148	Dominant	[redacted]

10mg/m2 (body surface area)				

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

B11. In CS, page125, it is explained that values for the length of time over which patients receive subsequent (second line) treatment were sourced from the published literature. Please explain whether these values were identified through a systematic literature review. Please clarify the process through which relevant literature was identified and selected.

A targeted literature review using Pubmed was conducted to identify the most recent and most relevant population inputs from official trial publications with longer follow-up data. To identify the relevant publications, terms such as 'CLL', 'second line therapy', 'relapsed/refractory (R/R) CLL' and 'clinical trial' were searched, along with the names of the drugs administered as second-line treatments to CLL patients. Since more than one publication was found for each treatment, only the most recent publication reporting the longest follow-up data was then selected.

B12. Please confirm that Table 36 and 38 contain PFS and OS estimates respectively, adjusted by the restriction of their hazard rates not exceeding background mortality. Please provide equivalent tables where the extrapolations are unadjusted by background mortality or any other constraint.

The question states that hazard rates do not *exceed* background mortality – this is incorrect. It can be confirmed that in the CS Document B, Table 36 and 38, on Pages 100 and 103 respectively, PFS and OS are adjusted by the restriction of their hazard rates *to not reduce below* background mortality. Table 40 provides the unadjusted landmark PFS estimates from the independent model. Table 41 provides the unadjusted landmark OS estimates from the dependent model.

Table 40: Unadjusted landmark survival for the individual model for PFS (independent model)

Distribution	VenG				GClb			
	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]							
Weibull	[redacted]							
Gompertz	[redacted]							
Log-logistic	[redacted]							
Log-normal	[redacted]							
Generalised gamma	[redacted]							

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Table 41: Unadjusted landmark survival for the dependent model for the OS (with treatment effect) model

Distribution	VenG	GClb

	5 year	10 year	20 year	30 year	5 year	10 year	20 year	30 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold indicates the base case.
Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; VenG: venetoclax with obinutuzumab

B13. Please provide the model output including coefficient value and the confidence interval around the estimate of the del17p/TP53 parameter in both the OS and PFS analyses used in the company base case.

Table 42 details the coefficient values and corresponding confidence intervals for the del(17p)/*TP53* mutation parameter as used in the base case OS and PFS extrapolations. Please note that for OS only one coefficient value is generated as the OS extrapolations are using dependent modelling.

Table 42: Coefficient values and corresponding confidence intervals for the del(17p)/*TP53* parameter as used in the base case OS and PFS extrapolations

Endpoint	Base case	Parameter	Estimate	Lower 95% CI	Upper 95% CI	SE
OS	Dependent model with exponential distribution	Rate	[redacted]	[redacted]	[redacted]	[redacted]
		Del(17p)/*TP53*	[redacted]	[redacted]	[redacted]	[redacted]
		Treatment	[redacted]	[redacted]	[redacted]	[redacted]
		VenG				
PFS	Independent model with log-logistic distribution	Shape	[redacted]	[redacted]	[redacted]	[redacted]
		Scale	[redacted]	[redacted]	[redacted]	[redacted]
		Del(17p)/*TP53*	[redacted]	[redacted]	[redacted]	[redacted]
		GClb				
		Shape	[redacted]	[redacted]	[redacted]	[redacted]
		Scale	[redacted]	[redacted]	[redacted]	[redacted]
		Del(17p)/*TP53*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival; SE: standard error.

B14. Please explain why PFS was not a suitable indicator for Time to Next Treatment, and why TTNT was modelled separately.

The CLL14 trial includes individual patient level data for VenG and GClb which contains data on both if and when patients received a next line of treatment. This information was translated into TTNT curves for VenG and GClb and subsequently used in the model. As became apparent from the CLL14 data, patients may not necessarily receive the next line of treatment immediately following progression, and this would not be captured when using PFS as a proxy for receiving a next line of therapy. This also aligns with UK clinical practice as confirmed by experts. Therefore,

the TTNT curve provides a more accurate picture of reality as observed in the CLL14 trial and was used in the model to predict TTNT. It should be noted that this observation from the trial data is to be expected and is in line with the BSH Guidelines which state: "Many patients with relapsed but asymptomatic CLL can be monitored with no therapy for a period of time."[20]

B15. Please explain why there are more patients on their next treatment than there are who have stopped their first treatment from months 2 to 5 for the VenG del17p/TP53 mutation population (according to the KM data in the economic model).

According to the data presented in Table 43, 3 deaths and 2 new anti-leukemic treatment (NLT) events occurred in the GClb arm, and 2 deaths and 2 NLT events in the VenG arm between month 2-6. The curve of GClb was higher because the time to death or NLT for the 5 subjects in the GClb arm was longer, compared with the time to death or NLT for the 4 subjects in the VenG arm; in particular, 2 subjects from the VenG arm went to NLT in around 2 and 3 months respectively, which makes the curve drop between Month 2–6.

Table 43: Event description of TTNT between month 2-6 by treatment arm

		GClb	VenG	Total
Death	Frequency	[redacted]	[redacted]	[redacted]
	Percent	[redacted]	[redacted]	[redacted]
New anti-leukemic treatment	Frequency	[redacted]	[redacted]	[redacted]
	Percent	[redacted]	[redacted]	[redacted]
Total	Frequency	[redacted]	[redacted]	[redacted]
	Percent	[redacted]	[redacted]	[redacted]

Abbreviations: GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

B16. PRIORITY: Please provide justification for constraining PFS hazard rates by background mortality.

The PFS curve represents patients who have CLL but have not progressed or died. Therefore, patients represented by the PFS curve should have an equal or higher hazard of dying from other causes (i.e., the hazards of background mortality generated from the lifetable), but logically must not have a lower hazard of dying than that of background mortality unless treatment for CLL is expected to lower the hazard of dying from other causes. To take account of this, the hazards of patients with CLL who have not yet progressed or died in the model should not be lower than the hazards of the general population mortality in the model and the PFS hazard rates are therefore constrained by background mortality.

B17. Please provide an assessment of proportionality between the ibrutinib data used in the company base case and the relevant CLL14 patients for PFS and OS, supporting the implementation of the hazard ratios in the economic model.

The log cumulative hazard plot of the log(-log(survival)) versus log of survival time is provided below for the naïve indirect comparison between the CLL14 trial and the Mato et al. publication, for both PFS (Figure 14) and OS (

Figure 15). The log cumulative hazard plots show no parallel lines; therefore, hazards are assumed to be non-proportional. It is important to recall that the sample size is very low in this analysis which could have influenced the assessment of proportionality and must be considered when interpreting both these assessments of proportionality and the results of the comparison.

Figure 14: Log cumulative hazard plot for PFS of ibrutinib versus VenG, using the Mato et al. publication

Abbreviations: IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab

Figure 15. Log cumulative hazard plot for OS of ibrutinib versus VenG, using the Mato et al. publication

Abbreviations: IBR: ibrutinib; OS: overall survival; VenG: venetoclax with obinutuzumab

Cost-effectiveness search

B18. Description of Identified Studies for HRQOL search (p173). It states that the excluded studies are presented in Table 13, Appendix G but this is the search strategy. Please clarify if this should be Table 20 on page 85: Publications excluded from the economic evaluation SLR at the full text screening stage.

The cross-reference on Page 173 of the CS Appendices for the list of records excluded at the full text review stage of the SLR incorrectly refers to Table 13 (Search terms for MEDLINE, Embase and EconLit [searched simultaneously via ProQuest]) on Page 65 in Appendix G. Please instead consider this cross-reference to be to Table 20 (Publications excluded from the economic SLR at the full text screening stage) on Page 85.

B19. Description of Identified Studies: Resource Use search (p210). It states that the excluded studies are presented in Table 13, Appendix G but this is the search strategy. Please clarify if this should be Table 20 on page 85: Publications excluded from the economic evaluation SLR at the full text screening stage.

The cross-reference on Page 210 of the CS Appendices for the list of records excluded at the full text review stage of the SLR incorrectly refers to Table 13 (Search terms for MEDLINE, Embase and EconLit [searched simultaneously via ProQuest]) on Page 65 in Appendix G. Please instead

consider this cross-reference to be to Table 20 (Publications excluded from the economic SLR at the full text screening stage) on Page 85.

Section C: Textual clarification and additional points

Missing references

C1. AbbVie Data on File (previously untreated CLL clinical SLR)

The source provided for Table 1 on Page 13, Table 2 on Page 14, and Table 3 on Page 14 of the CS Appendices incorrectly refers to a Data on File reference for the clinical SLR. The SLR referred to is that presented in full in the CS Appendices, and no such additional Data on File reference should have been cited here.

C2. On page 142 of the appendices, Table 23:

Cameron, H, 2014 *Canada*	GClb vs Clb	The CLL11 trial, data on file (Roche) and CLL5 trial were used

The data on file (Roche) comes directly from the publication source and describes what data has been used as a clinical source for the economic evaluation by Cameron. Hence, AbbVie does not have access to those data.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Clarification questions on addendum

March 2020

File name	Version	Contains confidential information	Date
1. ID1402 [ACIC]_VenG_Clarification Q_Part 2_Response	Final	Yes	10th March

Contents

Table of Tables

Table of Figures

Section A: Clarification on effectiveness data

A1. PRIORITY. The addendum provides updated PFS for the del(17p) subgroup and the TP53 mutation subgroup separately but not combined. Please provide updated results for the combined del(17p)/TP53 mutation subgroup (n=49), non-del(17p)/TP53 mutation subgroup (n=368) and missing subgroup (n=15) referred to in the clarification response A4.

Figure 8 of the addendum to the company submission presents the investigator-assessed progression-free survival (PFS) results by prognostic subgroup at the August 2019 clinical cut-off date (unstratified analysis). The forest plot shows updated PFS for the del(17p) and the *TP53* mutation populations separately. Figure 27 in Section A.3.3.8 of the addendum, however, presents the Kaplan–Meier plots for PFS for the combined del(17p)/*TP53* mutation population from the VenG arm of the CLL14 trial.

Table 1 presents the investigator-assessed PFS results for the requested subgroups from the August 2019 clinical cut-off and Figure 1–Figure 3 present the investigator assessed PFS Kaplan–Meier curves for the requested subgroups. Figure 8 of the addendum to the company submission presents the investigator-assessed progression-free survival (PFS) results by prognostic subgroup at the August 2019 clinical cut-off date (unstratified analysis). The forest plot shows updated PFS for the del(17p) and the *TP53* mutation populations separately. Figure 27 in Section A.3.3.8 of the addendum, however, presents the Kaplan–Meier plots for PFS for the combined del(17p)/*TP53* mutation population from the VenG arm of the CLL14 trial.

Table 1: Investigator-assessed PFS by del(17p)/*TP53* mutation status at August 2019 clinical cut-off date

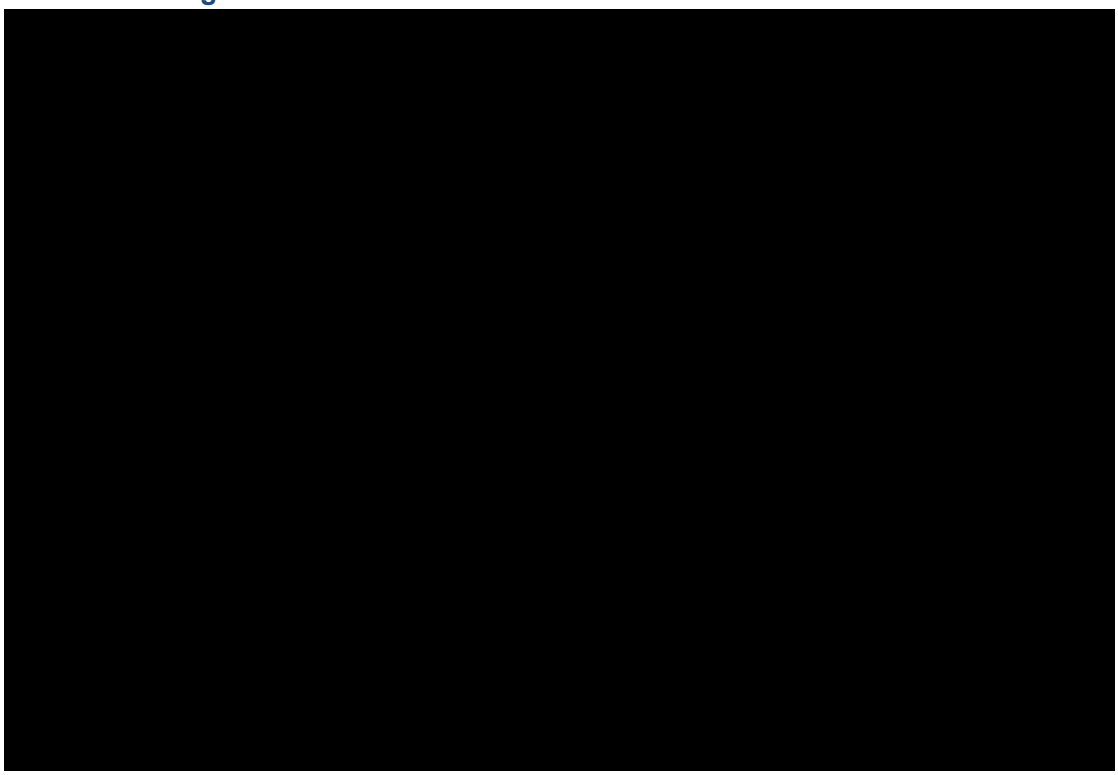
Subgroup	Total, n	GClb			VenG			Hazard ratio** (95% CI)
		n	Events	Median, months (95% CI*)	n	Events	Median, months (95% CI)	
Non-del (17p)/*TP53* mutation	368	184	[redacted]	[redacted]	184	[redacted]	[redacted]	[redacted]
Del (17p)/*TP53* mutation	49	24	[redacted]	[redacted]	25	[redacted]	[redacted]	[redacted]
Undefined mutation status	15	8	[redacted]	[redacted]	7	[redacted]	[redacted]	[redacted]

* 95% CI for median was computed using the method of Brookmeyer and Crowley.
** Hazard ratios were estimated by Cox regression model and stratified by Binet and Geographic region.
Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; NE: not evaluable; VenG: venetoclax with obinutuzumab.

Figure 1: Kaplan–Meier plot of investigator-assessed PFS for patients without del(17p)/*TP53* mutation at August 2019 clinical cut-off date

GDC-0199 refers to venetoclax.
Abbreviations: PFSINV: investigator-assessed progression-free survival.

Figure 2: Kaplan–Meier plot of investigator-assessed PFS for patients with del(17p)/*TP53* mutation at August 2019 clinical cut-off date



GDC-0199 refers to venetoclax.
Abbreviations: PFSINV: investigator-assessed progression-free survival.

Figure 3: Kaplan–Meier plot of investigator-assessed PFS for patients with missing del(17p)/*TP53* mutation status at August 2019 clinical cut-off date

GDC-0199 refers to venetoclax.
Abbreviations: PFSINV: investigator-assessed progression-free survival.

A2. PRIOIRITY. Please provide summary details of the specific interventions received as later lines of therapy by patients in CLL14, including how long patients received them for. Please provide information by treatment arm, and by del(17p)/TP53 mutation status. Additionally, please provide this summary information only for patients in the UK.

As noted in the addendum to the company submission, from the August 2019 clinical cut-off date, a [redacted] proportion of patients in the VenG arm ([redacted]) compared with the GClb arm ([redacted]) received new anti-CLL treatment after or before disease progression. [redacted] patients who received new anti-CLL treatment received it [redacted] disease progression ([redacted] of patients and [redacted] of patients in the VenG and GClb arms, respectively).

In the VenG arm, of the 9 patients who received new anti-CLL treatment after disease progression, [redacted] patients had received ibrutinib and [redacted] patients had received other treatments; [redacted] patients have received venetoclax as new anti-CLL treatment. In the GClb arm, after disease progression, [redacted] patients had received ibrutinib alone or in combination, [redacted] patients had received venetoclax alone or in combination; the remaining treatments received by more than one patient after disease progression were bendamustine with rituximab (BR) ([redacted] patients), R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/ prednisone; [redacted] patients), and rituximab ([redacted] patients).

Please note that CLL14 was a multicentre RCT conducted in 196 study locations in 21 countries. The study protocol did not include criteria for selection of next treatment, as such it was determined at the discretion of the investigator. Therefore, treatment options for later lines of

therapy may vary, depending on the reimbursement status of R/R CLL therapies and local clinical guidelines. The economic evaluation is required to comply as much as possible with UK clinical practice as per the NICE reference case. For that purpose, the economic model incorporates use and costs of subsequent treatments (type and proportion), aligned with UK practice and as advised by UK-based clinical experts at an AbbVie-organised advisory board and validated multiple times in subsequent clinician interviews.

The breakdown requested for all patients and for UK patients is presented in Table 2 below. The available data for later lines of therapy is limited, with most new anti-CLL therapies being administered to patients who received GClb ([redacted]) compared to VenG ([redacted]). For those treated with therapies which are administered continuously such as venetoclax and ibrutinib with missing treatment completion dates, it is assumed that patients are still ongoing treatment. The most used subsequent treatment was ibrutinib irrespectively of del(17p)/*TP53* mutation status. In addition, the data is insufficient on subsequent therapies specifically for patients based in the UK, with records showing [redacted] patient from the GClb arm without del(17p)/*TP53* mutation, ongoing subsequent treatment with ibrutinib. It is therefore preferable to model subsequent lines of therapy based on UK clinical practice.

Table 2: Summary details of the specific interventions received as later lines of therapy by patients in CLL14

	GClb (N=216)		VenG (N=216)	
	n (%)	Median Treatment Duration in Days (Range)ł	n (%)	Median Treatment Duration in Days (Range)ł
ALL CLL14 PATIENTS				
Patients receiving new anti-CLL treatment after or before disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Del(17p)/TP53*	[redacted]	[redacted]	[redacted]	[redacted]
Chemo or chemoimmunotherapy (CIT)				
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
Targeted Agents (alone or in combination)				
• [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]			[redacted]	[redacted]
Non-del(17p)/TP53*	[redacted]	[redacted]	[redacted]	[redacted]

		[redacted]		[redacted]
Chemo or chemoimmunotherapy (CIT)				
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]		
• [redacted]			[redacted]	[redacted]
Targeted Agents (alone or in combination)				
• [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
Undefined*	[redacted]	[redacted]	[redacted]	
Chemo or chemoimmunotherapy (CIT)				
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
• [redacted]	[redacted]	[redacted]		
Targeted Agents (alone or in combination)				
• [redacted]	[redacted]	[redacted]		
UK PATIENTS ONLY				
Patients receiving new anti-CLL treatment after or before disease progression	[redacted]	[redacted]	[redacted]	
Del(17p)/TP53	[redacted]		[redacted]	
Non-del(17p)/TP53	[redacted]	[redacted]	[redacted]	
Targeted Agents (alone or in combination)				
• [redacted]	[redacted]	[redacted]		

ǂ Cut-off dates are imputed as as end date of later lines of therapy for those administered continuously with missing end date. Treatment duration is calculated based on all later lines of therapy considering subjects may have multiple later lines of therapy.

* Please note the number of treatments can be greater than the number of patients receiving a subsequent line of therapy per patient subgroup given subjects may have received multiple next lines of therapy.
ǂ Subsequent treatment with GClb was performed out of protocol.
Abbreviations: BR: bendamustine with rituximab; CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukaemia; CVP: cyclophosphamide, vincristine and prednisone; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil with obinutuzumab; R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone; R-CVP: rituximab, cyclophosphamide, vincristine and prednisone.

A3: Please explain why the values provided in Addendum Table 3 for uMRD in peripheral blood 3 months after treatment completion (75.5% vs 35.2%) differ from the values provided in clarification response A7 Table 3 at FUM3 (71.8% vs 34.3%).

As described in section B.2.6.4 of the original company submission, MRD was measured in peripheral-blood at baseline, cycle 7-day 1, cycle 9-day 1, cycle 12-day 1 and then every 3 months thereafter. However, please note that there was also an end of treatment assessment (EOT), (i.e. 3 months after treatment completion/early termination). The values (75.5% [163/216] vs 35.2% [76/216]) presented in Table 17, page 47 of the original company submission and re-presented in the addendum to the company submission are based on EOT assessment, whereas the values ([redacted] vs [redacted]) provided in clarification response A7 Table 3 are based on the specific follow up month 3 (FUM3) visit. Please note the EOT assessment also accounts for subjects that discontinued prior to completing 12 cycles. Table 3 and Table 4 of clarification response A7 has been updated as Table 3 and Table 4 below to include the EOT assessment values.

Overall, as of the August 2019 clinical cut-off date, undetectable MRD (uMRD) rate in peripheral blood continues to be higher in the VenG arm compared with the GClb arm. At the 18-month follow-up visit, uMRD in peripheral blood was [redacted] in the VenG arm and [redacted] in the GClb arm. The difference in uMRD rates was [redacted] (95% CI: [redacted]).

Table 3: Undetectable MRD in peripheral blood over time for VenG

Timepoint	Undetectable MRD ($<10^4$)	Detectable MRD	PD/Death	Withdrawn	Missing
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C9D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C12D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C7D1: Cycle 7, Day 1; C9D1: Cycle 9, Day 1; C12D1: Cycle 12, Day 1; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PD: progressive disease; VenG: venetoclax with obinutuzumab. *EOT: End of treatment assessment - 3 months after treatment completion/early termination.

Table 4: Undetectable MRD in peripheral blood over time for GClb

Timepoint	Undetectable MRD ($<10^4$)	Detectable MRD	PD/Death	Withdrawn	Missing
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C7D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C9D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C12D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUM12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: C7D1: Cycle 7, Day 1; C9D1: Cycle 9, Day 1; C12D1: Cycle 12, Day 1; FUM: follow-up month; GClb: chlorambucil with obinutuzumab; MRD: minimal residual disease; PD: progressive disease; VenG: venetoclax with obinutuzumab. *EOT: End of treatment assessment - 3 months after treatment completion/early termination.

Section B: Clarification on cost-effectiveness data

B1. Please provide an update on section *'B.3.4.1 Health-related quality-of-life data from clinical trials'* in the original submission, where calculations and accompanying text are based on the latest data available (August 2019 data cut-off). Importantly, in the light of the latest data, please explain your choices on the source of utility data used in the economic model.

As explained in section B.3.4.1 of the original company submission, the estimated PFS utility values from CLL14 were presented to clinical and economic experts and were deemed to be infeasibly high thus, PFS and PPS utility values from a past appraisal (TA343) were used in the economic model.

Section 'B.3.4.1 Health-related quality-of-life data from clinical trials' in the original submission remains unchanged but values from Table 46 of company submission have been updated to CLL14 August 2019 values and are presented below for completeness (Table 5). For more detail on the methodology please refer to original company submission section B.3.4.1.

Table 5: Summary of estimated PFS utility values for Model 1 and Model 2

	With del(17p)/*TP53*	Without del(17p)/*TP53*
Model 1	[redacted]	[redacted]
Model 2 (with time)	[redacted]	[redacted]

Abbreviations: PFS: progression-free survival.

The PFS utility values from CLL14 that could be used for the non-del(17p)/*TP53* population are those estimated from model 2, which considers time as a relevant variable and thus is more in line with the progressive nature of this disease. For the del(17p)/*TP53* population, the PFS utility value that could be used is that estimated from model 1, as time is not a significant variable for this population.

With regards to the PPS health state utility values, due to the small sample size resulting in biased and uncertain estimates, these utility values are not recommended for use in the economic model. However, a breakdown of both the PFS and PPS utility values per subgroup have been provided in detail in response to clarification question B2 below.

As stated in response to question B1 of the first set of clarification questions, although it would have been AbbVie's preference to use EQ-5D values for CLL14, the utility values are not in line

with values commonly reported for CLL therapies and what has been previously accepted by NICE. This led to the conclusion that TA343 values are the next most appropriate source of evidence to inform the model's base case.

B2. Please provide utility scores calculated from EQ-5D-3L data collected in the CLL14 trial based on the latest data available (August 2019 data cut-off).

Please also refer to responses to B1 above and B3 below.

Table 6 presents the utility scores calculated from the EQ-5D-3L data collected in the CLL14 trial based on the August 2019 clinical cut-off.

The results from the PPS utility analysis need to be interpreted with caution, as in total only 35 patients progressed during the trial period, for whom there are only 65 responses. This very small sample size of EQ-5D-3L responses may cause some biases in the utility estimates and limit the ability to make any firm and reliable conclusion regarding the quality of life of patients in the PPS health state.

Table 6: EQ-5D-3L scores from the CLL14 trial at August 2019 clinical cut-off date

EQ-5D scores in CLL14	With del(17p)/*TP53*		Without del(17p)/*TP53*	
	VenG	GClb	VenG	GClb
Baseline (Cycle 1 Day 1)				
Number of responses/patients that responded	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free				
Number of observations	[redacted]	[redacted]	[redacted]	[redacted]
Number of eligible patients to respond	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard error)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression				
Number of observations	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients that responded	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard error)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: European Quality of Life 5 Dimensions; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

B3. On the basis of the latest available trial data (August 2019 data cut-off), please provide calculations showing the direction and significance of differences in mean EQ-5D utility scores between VenG and GClb in the non del(17p)/*TP53* population.

Please also refer to responses to B1 and B2 above.

The utility analysis was performed by fitting linear mixed effects models for repeated measures. The covariates included in the models were age, sex, treatment arm and time, to account for assessment point. Results showed that the treatment arm is not a statistically significant variable,

indicating that one (health state specific) utility value should be used in the economic model calculated as a weighted average of individual treatment arms.

Table 7 and Table 8 show the estimated coefficients of the parameters included in the utility regression for non-del(17p)/*TP53* mutation patients for PFS and PPS, respectively.

For the PFS utility analysis (Table 7), the coefficients for age, gender and time are statistically significant, while the coefficient for treatment arm is not significant, which means that treatment with VenG or GClb does not have a statistically relevant effect on the utility values. For the PPS utility analysis (Table 8), except from gender, the coefficients for the other variables are not statistically significant.

Table 7: Results from EQ-5D-3L PFS utility estimation (Model 2) for the non-del(17p)/*TP53* mutation population

	Coefficient	SE	d.f.	*t* statistic	*p* value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arm (VenG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of observations		[redacted]	Number of patients		[redacted]

Significance level: * 10%; ** 5%; *** 1%
Abbreviations: d.f.: degrees of freedom; EQ-5D-3L: European Quality of Life 5-Dimensions 3 Level Version; PFS: progression-free survival; SE: standard error; VenG: venetoclax with obinutuzumab.

Table 8: Results from EQ-5D-3L PPS utility estimation (Model 2) for the non-del(17p)/*TP53* mutation population

	Coefficient	SE	d.f.	*t* statistic	*p* value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arm (VEN+G)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of observations		[redacted]	Number of patients		[redacted]

Significance level: * 10%; ** 5%; *** 1%
Abbreviations: d.f.: degrees of freedom; EQ-5D-3L: European Quality of Life 5-Dimensions 3 Level Version; PPS: post-progression survival; SE: standard error; VenG: venetoclax with obinutuzumab.

As discussed in the response to Question B2, the results from the PPS utility analysis need to be interpreted with caution since these are drawn from only 35 patients that experienced a progression during the trial's observed period, for whom there are only 65 responses. This very small sample size of EQ-5D-3L responses may cause some biases in the utility estimates and limit the ability to make any firm and reliable conclusion regarding the quality of life of patients in the PPS health state.

Moreover, in all analyses presented, the coefficient of the treatment arm is not statistically significant, which suggests that any differences seen in values between treatment arms are not reliable. Instead a weighted average of the utility values for both treatment arms should be considered when exploring model scenarios with CLL EQ-5D data (Table 10 and Table 11).

B4. Please provide results from sensitivity analyses where health state utility values are treatment specific and non-treatment specific values available from the latest data cut-off (August 2019) of the CL114 trial.

Table 9 reports the health state utility values from the latest clinical data cut-off from the CLL14 trial.

Table 9: Health state utility values from CLL14 trial at the August 2019 clinical cut-off date

Treatment arm	PFS (IV treatment)	PPS*
With del(17p)/*TP53* mutation**		
VenG	[redacted]	[redacted]
Without del(17p)/*TP53* mutation		
VenG	[redacted]	[redacted]
GClb	[redacted]	[redacted]

*The utility values for PPS are based on a very small number of responses, particularly in the del(17p)/*TP53* mutation population (n=4). Only 35 patients progressed during the trial period, for whom there are only 65 responses and the EQ-5D utility data are therefore not interpretable.
**GClb is not a comparator for the del(17p)/TP53 mutation population; no changes have been made to the health utility values for ibrutinib as the data are not sourced from the CLL14 trial.
Abbreviations: GClb: chlorambucil with obinutuzumab; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; VenG: venetoclax with obinutuzumab.

As discussed in the original submission and in the responses to clarification questions B1 of the original questions and B1–B3 above, whilst it would have been AbbVie's preference to use EQ-5D values from CLL14, the values presented in Table 9 are not in line with values commonly reported for CLL therapies and those that have been previously accepted by NICE. The base case should continue to be considered as the conservative approach using data from TA343 as described in the response to the original clarification question B1.

Nevertheless, for completeness, results from cost-effectiveness model scenarios using the utility values shown in Table 9 have been calculated only to demonstrate that VenG is consistently a cost-effective option.

Table 10 and Table 11 presents the **list price** and **net price** scenario results respectively for incremental discounted costs, incremental discounted QALYs, ICER, and net monetary benefit for patients with del(17p)/*TP53* mutation and without.

Table 10: Cost-effectiveness scenario results based on list price utilising the utility values from the CLL14 trial at the August 2019 clinical cut-off date

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER, £/QALY	Net monetary benefit
Scenario 1: with del(17p)/*TP53* mutation VenG: PFS (IV) = [redacted], PPS = [redacted]				
Base case: with del(17p)/*TP53*	[redacted]	−0.163	[redacted]	[redacted]
Scenario 1: vs Ibrutinib	[redacted]	−0.436	[redacted]	[redacted]
Scenario 2: without del(17p)/*TP53* mutation VenG: PFS (IV and post IV*) = [redacted], PPS = [redacted] GClb: PFS (IV and post-IV*) = [redacted], PPS = [redacted]				

Base case: without del17p/TP53	[redacted]	1.057	Dominant	[redacted]
Scenario 2: vs GClb	[redacted]	0.052	Dominant	[redacted]

*The same utility value is also applied to post-IV since the literature post-IV utility value is less than the utility generated from the CLL14 trial while on IV.
**This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold. Positive NMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.

Table 11: Cost-effectiveness scenario results based on net price utilising the utility values from the CLL14 trial at the August 2019 clinical cut-off date

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER, £/QALY	Net monetary benefit
Scenario 1: with del(17p)/*TP53* mutation VenG: PFS (IV) = [redacted], PPS = [redacted]				
Base case: with del(17p)/*TP53*	−£280,896	−0.163	£1,727,509**	£276,018
Scenario 1: vs Ibrutinib	−£280,896	−0.436	£643,682**	£267,805
Scenario 2: without del(17p)/*TP53* mutation VenG: PFS (IV and post IV*) = [redacted], PPS = [redacted] GClb: PFS (IV and post-IV*) = [redacted], PPS = [redacted]				
Base case: without del17p/TP53	−£136,550	1.057	Dominant	£168,250
Scenario 2: vs GClb	−£136,550	0.052	Dominant	£138,110

*The same utility value is also applied to post-IV since the literature post-IV utility value is less than the utility generated from the CLL14 trial while on IV.
**This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold. Positive NMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.

B5. Similarly to your previous response to ERG's clarification question B10 (in document *"ID1402 Venetoclax Abbvie Clarif response v0.1 051219 PS [ACIC]*") please provide an alternative version of the model where Clb is administered over six cycles, on the basis of different doses and days of administration observed in UK clinical practice.

As explained in the response to B10 of the first round of clarification questions, there is variability in the dose and number of cycles of Clb used in UK clinical practice. Results based on the August 2019 data cut-off are presented below.

Since UK practice and guidelines on dose, number of cycles and days of administration vary, multiple versions of the ERG request have been provided for transparency:

- [B5] ID1402 (ACIC)_VenG_CLL_NICE Economic Model_Clb_6Cy_0.5mg
- [B5] ID1402 (ACIC)_VenG_CLL_NICE Economic Model_Clb_6Cy_10mg_D1,15
- [B5] ID1402 (ACIC)_VenG_CLL_NICE Economic Model_Clb_6Cy_10mg_D1-7

The **list price** and **net price** results are summarised in Table 12 and Table 13 respectively. Note that all the scenarios presented use a conservative cost calculation based on 6 cycles of Clb (as

requested by the ERG), even though some UK centres do use 12 cycles of Clb. Furthermore, these scenarios make an unjustified assumption of a full 12-cycle efficacy benefit of Clb as per the CLL14 trial outcomes as opposed to only a 6-cycle efficacy benefit of Clb which would be expected in these scenarios resulting in model outcomes that represent higher efficacy for the projected cost of Clb.

Nevertheless, even with this unjustified assumption on efficacy, VenG remains dominant in the non-del(17p)/*TP53* mutation population and differences in Clb administration do not have a meaningful impact on model outcomes.

Table 12: Cost-effectiveness model results at list price for the scenario where the GClb cost is aligned to UK clinical practice (efficacy remains as per CLL14)

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER, £ per QALY	Net monetary benefit
Scenario 1: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the CLL14 trial (0.5 mg/kg on Days 1 and 15) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	[redacted]	1.057	Dominant	[redacted]
Scenario 1: vs GClb	[redacted]	1.057	Dominant	[redacted]
Scenario 2: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the UK clinical practice dose (10 mg/m^2 on Days 1 and 15) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	[redacted]	1.057	Dominant	[redacted]
Scenario 2: vs GClb	[redacted]	1.057	Dominant	[redacted]
Scenario 3: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the UK clinical practice dose (10 mg/m^2 on Days 1 to 7) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	[redacted]	1.057	Dominant	[redacted]
Scenario 3: vs GClb	[redacted]	1.057	Dominant	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Table 13: Cost-effectiveness model results at net price for the scenario where GClb cost is aligned to UK clinical practice (efficacy remains as per CLL14)

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER, £ per QALY	Net monetary benefit
Scenario 1: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the CLL14 trial (0.5 mg/kg on Days 1 and 15) and efficacy based on 12 cycles as per CLL14 trial				

Base case: without del(17p)/*TP53* mutation	−£136,550	1.057	Dominant	£168,250
Scenario 1: vs GClb	−£136,217	1.057	Dominant	£167,916
Scenario 2: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the UK clinical practice dose (10 mg/m^2 on Days 1 and 15) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	−£136,550	1.057	Dominant	£168,250
Scenario 2: vs GClb	−£136,039	1.057	Dominant	£167,738
Scenario 3: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the UK clinical practice dose (10 mg/m^2 on Days 1 to 7) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	−£136,550	1.057	Dominant	£168,250
Scenario 3: vs GClb	−£136,533	1.057	Dominant	£168,233

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

B6. PRIORITY. There is a substantial difference between the mutation status subpopulations used in the CSR and CEM. Please provide:

- **i) the algorithms employed for assigning patients to mutation subpopulation in both CSR and CEM analyses,**
- **ii) an explanation of the reasons for the use of different classification algorithms for the CSR and CEM,**
- **iii) a version of the economic model where time-to-event analyses (PFS, time-on-treatment, time-to-new-treatment, the survival analyses of PFS and OS and incidence of AEs) are based on the mutation status subpopulations used in CSR (i.e. 49 patients).**
- **iv) please confirm that the reason for change in the number of patients categorised as 'undefined' from 14 to 10 between the original CS and the addendum (and the number with non-del(17p)/TP53 mutation increases from 387 to 391) is due to the error described in clarification responses A4 and A5.**
- **v) confirmation that following the company's algorithm for identifying patients eligible for the del(17p)/TP53 mutation subgroup, a patient without 17p deletion, but with TP53 mutation would not be included in this subgroup. (see original company submission section B.3.2.1) Please also provide justification for excluding patients with the TP53 mutation from this subgroup.**

The CEM analysis algorithm prioritises the del (17p) status, whereas the CSR analysis algorithm considers the del(17p) status and *TP53* status individually.

For clarity, Table 32 of the original submission has been updated to include the algorithms employed for assigning patients to mutation subpopulation in both CSR and CEM analyses and re-presented below (Table 14).

Table 14: Population numbers utilised in the CSR and CEM analyses (Table 32 of original submission)

	CSR analysis	CEM analysis
Non-del(17p)/*TP53* mutation	368	391
Del(17p)/*TP53* mutation	49	31
Undefined	15	10
Total	432	432
Algorithms	• If del(17p) is abnormal or *TP53* is mutated, variable = 1 • Else if del(17p) is normal and *TP53* is unmutated, variable = 0 • If del(17p) is missing & *TP53* is mutated, variable = 1 • If del(17p) is abnormal & TP53 is missing variable = 1 • Else if both are missing = NA (none have both missing)	• If del(17p) is abnormal (determined by central lab), variable = 1 • If del(17p) is normal (determined by central lab), variable = 0 • If del(17p) is missing & *TP53* is mutated, variable = 1 • If del(17p) is missing & *TP53* is unmutated, variable = 0 • Else if both are missing = NA

Abbreviations: CEM: cost-effectiveness model; CSR: clinical study report

A version of the economic model ([B6] ID1402 (ACIC)_VenG_CLL_NICE Economic Model) where time-to-event analyses are based on the mutation status subpopulations used in CSR (i.e. 49 patients) has been provided. Updates undertaken were on the following model areas:

1. All survival analyses of modelled populations and relevant AIC/BIC values using CSR grouping for all modelled outcomes of interest (ToT, TTNT, PFS, OS)
2. Incidence of modelled adverse events for the del(17p) subgroup calculated directly from corresponding CLL14 IPD data

The two model versions align on the trend of calculated ICER values for both the non-del (17p) (VenG dominant over GClb) and del(17p) subgroup (VenG is cost-saving compared to Ibrutinib with a positive NMB).

Specifically, for the non-del(17p) population, the new model version leads to slightly improved survival outcomes for both VenG and GClb attributed to assigning some of the previously included *TP53* mutated patients to the del(17p) group as per the CSR algorithm (see Table 15). VenG remains dominant over GClb but with a higher NMB compared to the previous model version.

Table 15 Non-del(17p): Comparison of impact on base case modelled outcomes: CSR vs CEM algorithm using CLL14 August 2019 data

	CSR (n=368)		CEM (n=391)	
	VenG	GClb	VenG	GClb
Progression free (years)	11.98	4.37	11.70	4.32
Post progression (Years)	2.33	9.93	2.44	9.82
Total life years	**14.30**		**14.14**	

Abbreviations: CEM: cost-effectiveness model; CSR: clinical study report; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

For the del (17p) model population, survival outcomes improved for both the VenG and Ibrutinib arms with a higher relative difference between PFS and OS compared to the previous model version (See Table 16). This led to a slightly higher NMB.

Table 16 Del(17p): Comparison of impact on base case modelled outcomes: CSR vs CEM algorithm using CLL14 August 2019 data

	CSR (n=49)		CEM (n=31)	
	VenG	Ibrutinib	VenG	Ibrutinib
Progression free (years)	6.94	9.43	5.82	7.46
Post progression (Years)	1.92	0.51	0.65	0.08
Total life years	**8.87**	**9.94**	**6.47**	**7.54**

Abbreviations: CEM: cost-effectiveness model; CSR: clinical study report; VenG: venetoclax with obinutuzumab.

In conclusion, results between the two model versions are comparable. When modelling according to the CSR algorithm, survival outcomes improve for all treatment arms and VenG remains dominant compared to GClb and cost saving compared to Ibrutinib.

We can confirm that the number of patients categorised as having undefined del(17p)/*TP53* status is as described in the CSR corrigendum (also explained in the response to questions A4 and A5 of the original set of clarification questions).

A patient without del(17p), but with *TP53* mutation would not be included in the del(17p) */TP53* subgroup as per the CEM patient allocation to each of the two modelled populations. When following the CSR algorithm, aforementioned cases would indeed be included in the *TP53* and or del (17p) population.

B7. Please can you add to the economic model the option to implement the comparison of ibrutinib to VenG using the pooled data of patients from Mato et al., Ahn et al. and Woyach et al. publications for PFS, and from Mato et al. and Ahn et al. for OS.

VenG versus ibrutinib – patients with del(17p)/TP53 mutation

The NICE Decision Support Unit (DSU) Technical Support Document 18[1] on population-adjusted indirect comparisons states that naïve comparisons are prone to bias and should be treated with caution in decision making, as these estimates are very likely to be misleading and not reflective of the true effect of treatments.[2] When feasible, a matching adjusted indirect comparison (MAIC) using prognostic factors and effect modifiers should be preferred over any naïve unadjusted comparisons and their pooled estimates.

Unfortunately, given the paucity of evidence, any scenarios attempted and presented for the subgroup of del(17p)/*TP53* can only compare data naively, and therefore the results from these analyses cannot be considered methodologically robust. We do not believe that a pooled estimate will be more informative than the individual Mato et al.[3] and Ahn et al.[4] estimates submitted in the original company submission and Addendum. Specifically, our position is that all analyses will be prone to bias and that, in the absence of a MAIC, decisions should be based on a collective trend rather than a point estimate.

Although Woyach et al.[5] was not considered as an individual source due to a small sample size (<10 patients for the subgroup of interest), a pooled analysis of all three sources was attempted as per request and allowed us to confirm that VenG is a cost-effective option for patients with del(17p)/*TP53* mutation.

An option was added to the economic model to accommodate this request ([B7] ID1402 (ACIC)_VenG_CLL_NICE Economic Model). The hazard ratios listed in Table 17 were obtained in the following steps:

- The Kaplan–Meier curves for PFS (Ahn, Mato, Woyach) and OS (Ahn, Mato) were digitised
- From the digitised curves, patient-level survival data were simulated using the Guyot et al.[6] algorithm
- The patient-level datasets for ibrutinib were merged as if they were one trial (i.e. no adjustments for effect modifiers or confounders have been made)
- The patient-level data for VenG was added to this dataset
- A cox proportional hazard model was fitted onto the patient-level data to estimate the hazard ratio of ibrutinib versus VenG.

The Kaplan–Meier curves for OS and PFS are shown in Figure 4 and Figure 5.

Table 17: HRs for PFS and OS based on pooled patient-level data

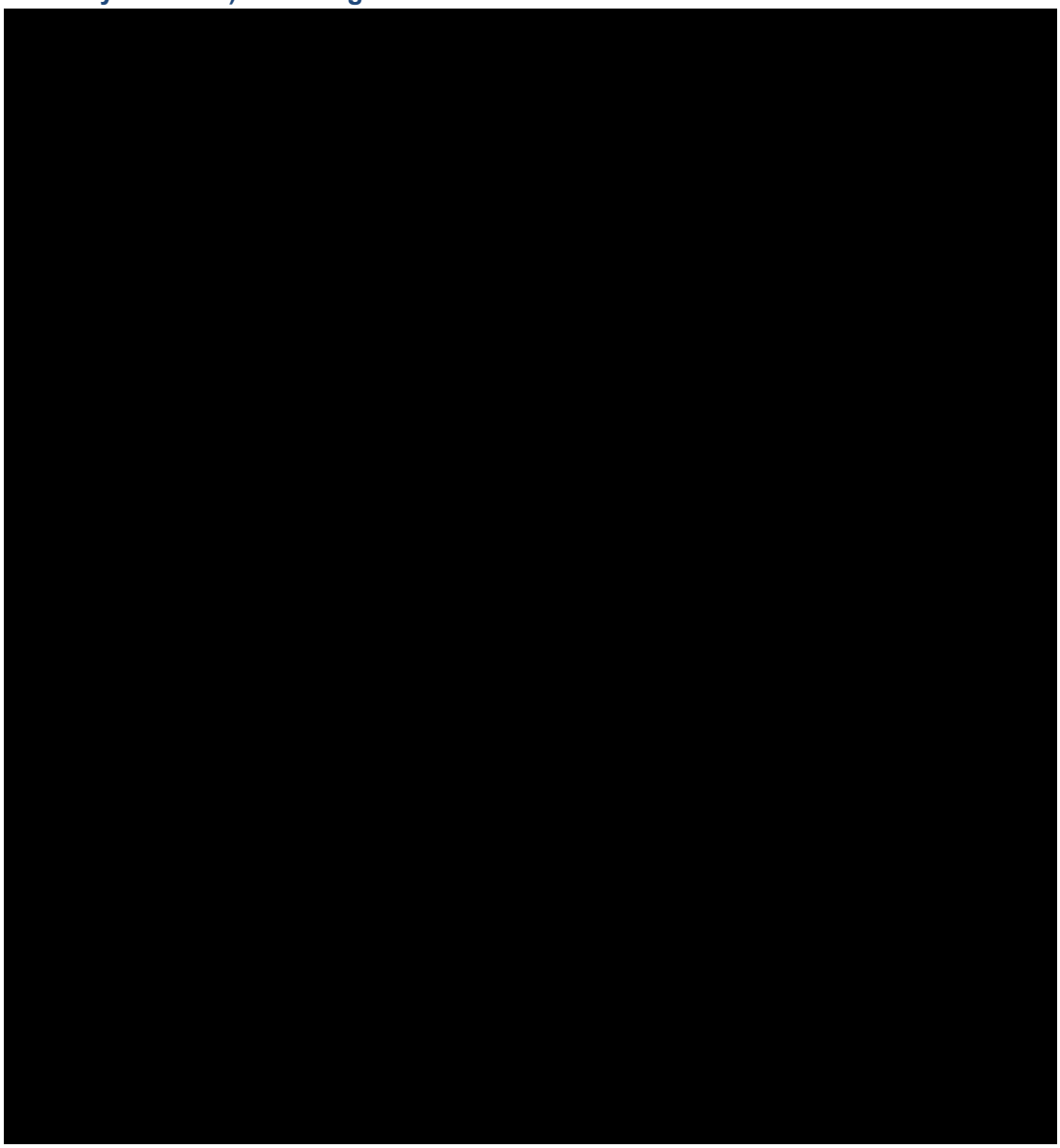
Ibrutinib versus VenG	HR	CI 2.5%	CI 97.5%	SE ln(HR)	P value
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; SE: standard error; VenG: venetoclax with obinutuzumab.

Figure 4: OS for VenG (CLL14) and ibrutinib (pooled from Mato et al. and Ahn et al.) including 95% CIs

Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; OS: overall survival; VenG: venetoclax with obinutuzumab.

Figure 5: PFS curves for VenG (CLL14) and ibrutinib (pooled from Mato et al., Ahn et al. and Woyach et al.) including 95% CIs



Abbreviations: CI: confidence interval; HR: hazard ratio; IBR: ibrutinib; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

It must be noted that there are several caveats to pooling the Ibrutinib data and applying the obtained hazard ratio:

- Ahn et al., Mato et al. and Woyach et al. reported survival outcomes, but no baseline characteristics specific to the del(17p)/*TP53* mutation subgroup. Therefore, it cannot be assessed whether pooling these survival data is valid, nor whether a comparison of these data to VenG is valid.
- The patient population from Woyach et al. contains only nine patients, of whom two experienced an OS event.
- As visible in the Kaplan–Meier curves, many patients are censored in the ibrutinib arm. After 20 months, only ~50% of the patients are still at risk.

- As visible in Figure 4 and Figure 5, the survival curves cross, indicating the proportional hazards assumption does not hold.
- Survival data are very immature as median survival is not reached during the study period.

Overall, it is not possible to detect and describe the level of bias of those estimates (qualitatively or quantitatively) and heterogeneity between pooled populations in the absence of information on prognostic factors and effect modifiers.

We are unable to say whether the level of relative difference in efficacy between VenG and ibrutinib will also be seen in clinical practice, but we can reliably state that VenG is effective in del(17p)/*TP53* patients (as evidenced in the CLL14 trial) and cost saving compared to ibrutinib. In addition, treatment options aside from ibrutinib are very limited and there is a high unmet need for patients who cannot tolerate ibrutinib, such as those with significant cardiac disease or bleeding risk.

B8. Please explain the rationale for calculating the costs of later lines of therapy for ibrutinib patients inconsistently in comparison to VenG and GClb patients. (i.e. costs appear to be applied to new incidences of disease progression or death, instead of applied to a "time on next treatment" period).

The questions states "time *on* next treatment", however this was assumed to be a typo and the response to this question provides an answer based on modelling time *to* next treatment. Time *on* subsequent therapies is defined by the specified subsequent therapy as described in the original CS, Tables 56 and 57, and the approach taken is not inconsistent between comparators.

Patient level data from the CLL14 trial was used to inform the time to next treatment (TTNT) curves for VenG and GClb in the CEM analyses as the best available source of data to most accurately inform the observed effects seen in CLL14 trial for both arms. However, publicly available patient level data to inform TTNT curves for ibrutinib were not identified. Therefore, PFS and OS curves were used instead as the next best available source of evidence to inform which patients might progress to next line treatment, after ibrutinib treatment as a first line therapy.

B9. Please explain why for the del(17p)/TP53 mutation population in the VenG arm, there appears to be more patients who have begun their next anti-leukemic therapy than who have stopped receiving first line treatment (i.e. TTNT is less than ToT from 1.84 months until 4.60 months in columns P and AI of "KM Data sheet"). The ERG anticipates that there should not be an overlap period of first and second-line therapy.

The discrepancy observed in the first and second line therapies between 1.84 months to 4.60 months is primarily due to the way 'death' is censored for ToT and TTNT. For ToT, patients whose treatment duration was equal to time of death or loss to follow up were censored. For TTNT, death and new anti-leukemic treatment were considered events and other patients were censored. This leads to TTNT estimates that are lower than ToT estimates between 1.84 months to 4.60 months. Additionally, with only a few patients and few events in the TTNT curve for the del(17p) subgroup, small changes have a larger impact on the survival probability.

This discrepancy is explained by difference in definition of outcomes and does not lead to inconsistent results. For clarity, ToT curves are only utilized for costing purposes of VenG and GClb over the first 12 cycles and calculations are applied consistently between arms using Kaplan–Meier data from CLL14.

B10. Please present hazard ratios and Kaplan-Meier plot of TTNT analyses when death events are instead censored at time of death, and allow this alternative modelling of TTNT to be specified in the economic model.

Figure 6presents the Kaplan–Meier plot and hazard ratio of TTNT analyses when the death events are censored.

Figure 6: Kaplan–Meier plot for TTNT when death events are censored

Abbreviations: GClb: chlorambucil with obinutuzumab; TTNT: time-to-next treatment; VenG: venetoclax with obinutuzumab.

An updated model ([B10] ID1402 (ACIC)_VenG_CLL_NICE Economic Model) has been provided which allows alternative modelling of TTNT to be specified i.e. death events are censored at time of death. This approach leads to an improved hazard ratio compared to that submitted in base case however, this has a minimal impact on the ICER values generated in either model population. This option is provided for completeness but is not considered appropriate to inform the model's base case. We suggest that analyses are based on exact CSR curves for TTNT with no additional censoring to ensure that effect seen in trial follows ITT sample as normally expected when modelling KM data.

B11. Please can you add to the economic model the option to model time on next treatment for ibrutinib patients equivalently to VenG patients with the del(17p)/TP53 mutation subpopulation to allow for an alternative analysis when comparing to ibrutinib.

The questions states "time *on* next treatment", however this was assumed to be a typo and the response to this question provides an answer based on modelling time *to* next treatment. Time *on* subsequent therapies is defined by the specified subsequent therapy as described in the original CS, Tables 56 and 57, and the approach taken is not inconsistent between comparators.

As mentioned in response to question B8 above, it was not possible to model the time to next treatment for ibrutinib in the same way as VenG (i.e. by using TTNT). Instead, PFS and OS curves were used to inform which patients might progress to the next line treatment, following ibrutinib treatment as a first line of therapy. Differences between VenG and Ibrutinib are with respect to the costing approach (incidence-based in each model cycle from TTNT data vs. cumulative from PFS Ibrutinib curve respectively) and timing of when the costs of subsequent line of therapy occur in the model calculations between arms.

It was not possible to crudely apply the VenG arm TTNT curve to the Ibrutinib one since this lies consistently under the Ibrutinib PFS curve (see model representation below; Figure 7) which means this is clinically implausible (Approach 1 as per ERG suggestion).

Figure 7: TTNT and PFS data for VenG and Ibrutinib

Abbreviations: CI: confidence interval; GClb: chlorambucil with obinutuzumab; HR: hazard ratio; Ibr: Ibrutinib; KM: Kaplan-Meier OS: overall survival; PFS: progression-free survival; SE: standard error; TTNT: time to next treatment; Ven + G: venetoclax with obinutuzumab.

However, we have provided an alternative approach (Approach 2) using the per cycle difference between the VenG PFS and VenG TTNT curves and applied this difference to calculate Ibrutinib subsequent treatment costs as done for the VenG arm. On average, the difference between the PFS and TTNT curves for VenG patients was 0.055 years as per model calculations.

Both approaches (Approach 1 and Approach 2) described above have conceptual limitations that do not lead to sensical model outcomes. This model behaviour is mainly due to TTNT and PFS being highly correlated in CLL and driven by maintaining patients in progression-free survival. It is therefore clinically and methodologically inappropriate to apply the TTNT curve from the VenG arm to the Ibrutinib arm given the differences in PFS seen between the two arms (Ibrutinib vs VenG as per the Mato calculated PFS HR=0.660).

Specifically, Approach 2 that was incorporated in the model's cost calculations leads to inconsistent model behaviour where patients in the Ibrutinib arm spend less time in PPS compared to VenG but incur more subsequent treatment costs. See Figure 8 below where the issue in model behaviour has been isolated.

Figure 8: Model results for subsequent treatment modelled outcomes and corresponding treatment costs for approach 2

	VenG	Ibrutinib
Post progression survival (years)	0.65	0.08
Subsequent treatment costs	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]

Abbreviations: VenG: venetoclax with obinutuzumab.

The addition of the proxy TTNT per cycle estimates only impacts the subsequent treatment costs for Ibrutinib. Ibrutinib becomes more expensive and there is no change to efficacy outcomes. These results are by no means plausible and cannot be considered informative.

We do not believe that there is a meaningful way of regenerating the Ibrutinib TTNT curve using VenG data and continue to support the method employed in the original company submission as most informative of Ibrutinib efficacy.

This option to apply approach 2 as a scenario within the model is nevertheless provided as a model version ([B11] ID1402 (ACIC)_VenG_CLL_NICE Economic Model) and can be tested as follows:

a. When the 'Unfit 1st line CLL Only Del(17p)' subgroup is chosen in the 'Main board'

b. Under 'Cost settings' and 'Include subsequent treatment (tx) costs' the user is able to choose the option 'Ibrutinib: Use VenG TTNT'.

B12. Please provide an assessment of proportionality between the ibrutinib data used in the company base-case and the VenG patients present in del(17p)/TP53 mutation subgroup as classified by the CSR of CLL14, for PFS and OS.

The ibrutinib data used in the company base-case considered data from the Mato et al study.[3] The hazard ratios for PFS and OS versus Mato et al. used in the submission were estimated using the del(17p)/*TP53* mutation subgroup definitions as in the CSR, because the CSR definition aligned with the definition used by Mato et al[3] and Ahn et al.[4] The validity of the proportional hazards assumption was tested using a Schoenfeld residuals test.

The survival curves for PFS and OS cross multiple times, indicating that proportionality of hazard cannot be assumed (Figure 9 and 10 in the company submission). A statistical test of the proportionality of the treatment effect coefficient (using the cox.zph() function in R) did not give reason to reject the proportional hazards assumption (Table 18). However, the statistical test is likely underpowered due to the small sample size and the trend in relative treatment effect over time, as observed in the Schoenfeld residuals plots (Figure 9 and Figure 10), indicate that proportional hazards can likely not be assumed.

Table 18: Results from the proportionality test

	Rho	Chi-squared	p value
PFS HR	[redacted]	[redacted]	[redacted]
OS HR	[redacted]	[redacted]	[redacted]

Abbreviations: HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

Figure 9: Schoenfeld residuals plot for ibrutinib versus VenG for OS (Mato et al.)

Abbreviations: IBR: ibrutinib; OS: overall survival; VEN+G: venetoclax with obinutuzumab.

Figure 10: Schoenfeld residuals plot for ibrutinib versus VenG for PFS (Mato et al.)

Abbreviations: IBR: ibrutinib; PFS: progression-free survival; VEN+G: venetoclax with obinutuzumab.

B13. Please reproduce Figure 26a and 26b from the original company submission, but including patients as classified by the CSR of CLL14.

Figure 11 presents the Kaplan–Meier curves for OS and PFS for VenG and GClb by del(17p)/*TP53* mutation population as classified by the CSR of CLL14.

Figure 11: Kaplan–Meier curves for OS and PFS stratified by treatment arm and del(17p)/*TP53* mutation status

Abbreviations: GClb: chlorambucil with obinutuzumab; OS: overall survival; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

B14: Please clarify why the company maintained the inclusion of the treatment coefficient in the modelling of OS when no significant difference was found.

Inclusion of the treatment coefficient in modelling of OS allows the model user the option to assume a treatment effect on OS between VenG and GClb (although this is currently not assumed; please see response to Question B15). We do reflect that including the treatment coefficient is not relevant to the August 2019 cut-off where OS was found to be [redacted] between arms (OS HR=[redacted]; CLL14 August 2019) but this wasn't the case in the previous cut-off (OS HR=1.24; CLL14 August 2018). Adding treatment as a coefficient has previously informed conclusions on proportional hazards assumption and on the trend in OS from CLL14 in order to decide on the appropriate base case.

B15. Please clarify why the company set the OS for VenG to be equal to the OS for GClb. Please can you add to the economic model the option to use the OS extrapolation for VenG for both arms instead.

The OS data from the CLL14 trial are immature and the median OS [redacted] in either the GClb or VenG arms. To maintain a conservative approach, we did not want to rely solely on extrapolations based on immature data and very few events (as observed in the VenG arm). Therefore, multiple clinicians were consulted to gauge current clinical opinion on the difference in OS between the VenG and GClb treatment arms. Based on clinical opinion from three clinicians (two UK and one US [affiliated with the CLL14 trial]), assuming no treatment

effect on OS and using the GCIb OS curve was deemed the most conservative approach to modelling the OS curve of VenG, as the GCIb curve has more events.

Due to time-restrictions in replying to these clarification questions updated results have not been presented in this response. However, given that the OS curves from the August 2019 clinical cut-off date are almost identical between the VenG and GCIb arms (please see CSR and Figure 17 of the Addendum), ICER values using the VenG curve from the CLL14 trial are expected to be almost identical to current outcomes. Therefore, we do not anticipate any impact on the underlying cost-effectiveness results.

B16. Please clarify the reason for the discrepancy between the TLS risk distribution numbers (%) in CS Table 54 and the numbers given in the text preceding the table. Interestingly, the numbers given in the text of the original submission (based on the 2018 data cut off) are the same as the updated numbers (%) in the text and table that you provided in the addendum document (based on the August 2019 cut off). Can you please confirm if the relevant numbers (%) in the addendum document are correct.

The TLS rates in the original company submission (August 2018 clinical data cut-off) were based on the number of patients in the VenG and GCIb arms who had been treated with VenG and GCIb, respectively, instead of the ITT population. To maintain consistency with the Fischer et al (2019)[7] publication and all the analyses in the economic model, the sample size per treatment arm has been updated to the ITT sample size (i.e. n=216 for both arms).

TLS rates and costs were updated using Fischer et al. (2019)[7] and the August 2019 clinical cut-off data. For reconfirmation, Table 19 presents the TLS distribution being used in the economic model. This addendum does not have a substantial impact on model outcomes and underlying cost-effectiveness results.

Table 19: TLS risk distribution for VenG and GCIb treatment arms

Treatment	Lower risk (node diameter ≤5 cm and ALC <25 x 10^9)	Greater risk (node diameter >5 cm or ALC >25 x 10^9)	
		Creatinine clearance > 80 mL/min	Creatinine clearance ≤ 80 mL/min
VenG	[redacted]	[redacted]	[redacted]
GCIb	[redacted]	[redacted]	[redacted]

Abbreviations: ALC: absolute lymphocyte count; GCIb: chlorambucil with obinutuzumab; TLS: tumour lysis syndrome; VenG: venetoclax with obinutuzumab.

Section C: Textual clarification and additional points

No comments to add.

References

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2. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011;14:417-28.
3. Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. Am J Hematol 2018;93:1394-1401.
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5. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med 2018;379:2517-2528.
6. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
7. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. New England Journal of Medicine 2019;380:2225-2236.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Chronic Lymphocytic Leukaemia Support (CLLSA) in collaboration with Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Chronic Lymphocytic Leukaemia Support Association (CLLSA)** is a national patient led charity run by volunteers and was formed in 2005; it is the only UK Chronic Lymphocytic Leukaemia (CLL) specific support charity. The charity's remit is to provide support to people affected by CLL and its subtypes by keeping them informed of recent and relevant developments in CLL, treatment and research and to provide opportunities for awareness raising and mutual support. This requires the association to support and aid empowerment through education while advocating for improving outcomes and access to better treatments. CLLSA provides support to the UK CLL community and CLLSA membership of 3,000+ association members who live with CLL or are carers and the 13,000+ CLLSA on-line community members (not all UK based) on the Health Unlocked platform. CLLSA provides up to 6 patient conferences a year. CLLSA support patients through telephone and email, one to one at meetings, literature in the form of patient information packs, newsletters and the websites: http://www.cllsupport.org.uk and https://healthunlocked.com/cllsupport . The association is funded by member's donations, legacies, members' fund raisers and unrestricted educational grants from some pharmaceutical companies. *** **Lymphoma Action** is a national charity registered in England and Wales and in Scotland (see www.lymphoma-action.org.uk). Our primary aim and objective is to provide information, advice, support and training to everyone affected by lymphoma. We work throughout the UK, publishing leading, quality-assured written information on lymphoma,

	operating a clinical trials information service (Lymphoma Trials Link at www.lymphomas.org.uk/lymphoma-trialslink and providing a national helpline, a network of support groups and a buddy scheme. We have launched a well-being programme specifically designed for those with lymphoma (Live Your Life). We also provide education and training courses for healthcare professionals, as part of their CPD. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. Lymphoma Action is not a membership organization.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**CLLSA as follows**: Novartis £ 5,000 sponsorship for patient conferences Gilead £11,000 for core services funding and sponsorship of patient conferences Janssen £10,000 core services funding and sponsorship funding of consultancy work Abbvie £10,000 core services funding Roche £15,000 Sponsorship of newsletter, website and patient conferences **Lymphoma Action as follows:** AbbVie £10,000 sponsorship of education and training/survivorship events; publications; core services Roche £20,000 sponsorship of education and training/survivorship events; publications; core services Gilead £38, 000 sponsorship of education and training/survivorship events; publications; core services Janssen £15,000 sponsorship of education and training/survivorship events; publications; core services
4c. Do you have any direct or indirect links with, or funding	No, none for either CLLSA or Lymphoma Action organisations.

from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was obtained via an online survey, social media and online forums asking for information from patients who have been diagnosed, in treatment or remission from CLL. It was conducted by the CLL Patient Advocacy Group (CLL PAG) and The Leukaemia and Lymphoma Society of Canada. 212 responses were received from patients wordwide. In addition, two care giver surveys were used to which 33 responded and 92% were female. A separate and specific on line tool was used for a survey which was distributed in June 2017 for CLL patients who have received Venetoclax and there were 28 respondents. The tool used the EQ-5D Quality of Life questions with some supplementary questions regarding length of Venetoclax treatment.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	CLL is a complex disease to understand let alone diagnose. It takes an average of around 3 months from onset of symptoms (if the patient has any) to diagnosis and it can require repeated visits to healthcare professionals. This causes frustration and has a significant emotional impact; people affected know something is wrong but it can take a long time to confirm what that is. This impact continues throughout the treatment pathway for both patient and carers. In our surveys common symptoms reported at diagnosis include fatigue (51.6%), increased lymphocyte count (48%), enlarged lymph nodes (39.1%), frequent infections (21%), night sweats (19.4%), enlarged spleen or discomfort on upper left side of stomach (15.7%), shortness of breath (15.3%), anaemia (13.7%), thrombocytopenia (10.5%), pain (8.1%), fever (5.6%) and neutropenia (5.2%). In around 7 in 10 cases, CLL is discovered by chance during investigations for something else. This can be psychologically challenging for patients. Most people have not heard of CLL before their diagnosis. Once diagnosed, they are likely to focus on the ‘leukaemia’ aspect, as they understand this as a form of cancer. More often than not, there is not sufficient

	focus on the chronic, long-term nature of the disease. The most common approach to managing CLL is active monitoring. This is a challenge for people to understand and come to terms with. They have a cancer diagnosis but there is not any immediate treatment action. While approximately one third of patients experience few symptoms at diagnosis, almost all will develop increasing symptoms as their disease progresses. Two thirds will be monitored under “watch and wait” (active monitoring) whilst their disease progresses until treatment is necessary because of an increasing and uncomfortable symptom burden. The other third will require treatment not long after or immediately after diagnosis. The negative emotional and psychological issues experienced at diagnosis remain high for the majority of patients during the watch and wait period: “stress” (75.8%), “anxiety” (59.3%), “difficulty sleeping” (38.7%) and “depression” (30.6%). Patients worry about relapse, knowing further toxic treatment is likely to impact negatively on their quality of life. For almost all patients, CLL is incurable. Patients can be left living with a significant symptom burden and poor quality of life, uncertain as to what will happen next, waiting until there is a further decline in their wellbeing and clinical assessments, before treatment is started. Any treatment usually ends in eventual relapse so patients live in a cycle of ‘waiting, treatment then relapse’, which is repeated and continues until death. CLL tends to respond less well to each line of therapy, with shorter subsequent remissions. Around 85% of patients diagnosed aged 65 or older and many also have comorbidities., This means the more toxic treatments are not well tolerated by the majority of patients. As CLL is a genetically evolving disease, many patients are also concerned that they could experience Richter’s transformation to an acute form of lymphoma, which is a rapidly progressing and generally an ‘end of life’ event. This occurs in approximately 10% of patients. Patients with CLL have an increased risk of infection, as their immune system is severely compromised by the disease even during the watch and wait phase. These frequent and persistent infections impact hugely on quality of life, as well as being a leading cause of death for CLL patients. During the winter, many patients, and their families, experience long periods of isolation to try to reduce the risk of infection. As outlined above, living with CLL is difficult and does not affect the patient alone, but instead creates a

	“ripple effect”, impacting on the whole family and even friends and colleagues. Family members/carers can be challenged with exhausting caretaking duties when someone they know is diagnosed with CLL. Carers cited having to take on previously shared household duties. Many had to give up their own jobs, adding to the negative financial impact that living with CLL can cause. Patients’ compromised immune systems and treatment side effects were cited by 20% of carers as a reason for reduced social contact with family and friends for both caregivers and patients. Some sacrificed holidays and non-essential social events because of it. **Patients report:** "it's so difficult to plan anything, especially holidays, as I have no idea if I'll be well enough to go. Insurance is another expensive problem" "I worry about catching flu as I can't make antibodies myself and so I tend to stay away from people during winter." "My wife worries so much about what might happen next, she doesn't say anything to me but she tells our children who then worry too" Living with CLL is living with uncertainty for both the patient and carer – uncertainty about disease progression, length of life, quality of life, possible infections and an inability to live a ‘normal’ life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	CLL is incurable and treatment goals and strategies need to be selected to suit individual needs depending on treatment history, overall health, fitness, co-morbidities risk and patient choice. Treatment may be chemotherapy, targeted biologicals, monoclonal antibodies, BCR inhibitors, steroids and finally, supportive care for end of life. CLL patients often require repeated treatments as the CLL relapses. They generally respond less well, with shorter remissions, to each subsequent line of therapy. Fitter patients are usually able to tolerate the more toxic chemotherapy regimens aimed at achieving durable remissions and, ideally, undetectable disease. However, this is often at the expense of QOL and may mean hospital admissions and cumulative toxicities over their lifetime, including the risk of future

	myelodysplasia and acute myeloid leukaemia. Less fit patients have to aim for extending their 'time to next treatment' using more tolerable treatments, which are often less effective and do not give long remissions. It is known that patients with high risk genetics, 17p deletions and TP53 aberrations, do not have durable responses to chemo based regimens and would be treated first line with Ibrutinib. The introduction of targeted therapies has provided treatment options that have improved survival and quality of life for these groups. However, Ibrutinib is contraindicated for some cardiac patients and those who need to take anticoagulants. Idelasilib has a toxicity profile that many find unacceptable. Patients who experience disease progression or relapse after these therapies, or who have to discontinue due to side effects, have a dismal outlook. Patients for whom treatment with Ibrutinib/Idelalisib is not an option because of co-morbidities have extremely limited options if they cannot tolerate chemotherapy. For these, generally elderly patients, anti CD20 antibody therapy or best supportive care (BSC) may be the only options. Whilst BSC may treat symptoms or disease complications, it does not actively treat the CLL. As such, BSC leads to disease progression and ultimately death. There is clearly an urgent unmet clinical need that Venetoclax and Obinutuzumab would treat. Venetoclax and Obinutuzumab offers a highly effective and time limited treatment with the possibility of undetectable residual disease which, it is hoped, will translate into a durable remission and treatment free period. We cannot overstate the importance and the need for a range of treatment options for patients with CLL given the heterogeneity of both the disease and patient population.
8. Is there an unmet need for patients with this condition?	Patients for whom treatment with Ibrutinib/Idelalisib is not an option because of co-morbidities have extremely limited options if they cannot tolerate any type of chemo-immunotherapy. For these patients, anti CD20 antibody therapy or best supportive care (BSC) may be currently the only options. Because of the heterogeneous nature of the CLL a wide range of treatment options is important and there is an unmet need for an effective, time limited treatment that can produce durable remissions with few side effects. This is irrespective of patient co-morbidities. Venetoclax and Obinutuzumab meets that unmet need.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients are aware of the CLL14 study and consider Venetoclax and Obinutuzumab to be a step change for all patients who are having their first therapy. This time limited treatment combination gives all patients, irrespective of their genetic markers (del17p or mutTP53), the potential to achieve negativity for any residual disease and a long period of remission. Venetoclax and Obinutuzumab is a clinically effective treatment, with a favourable tolerability profile, high response rates and symptom control. Clinical trials and patient reports show that the combination results in a significant improvement in the quality of life of patients and their families. The treatment is very convenient, with Venetoclax being an oral therapy that can be taken at home after the initial dose ramp up which may be initiated in hospital. The Obinutuzumab infusions are hospital based. Patients reported that knowing that this is a time limited, effective therapy is an attractive consideration. Importantly, patients' anxiety, and that of their families and carers, has reduced significantly knowing that they are receiving an effective, non-toxic treatment. The responses indicated that the burden of care on the family and care givers is likely to be much reduced for patients taking Venetoclax. The anxiety of a possible early relapse has a severe impact on family and relationships, so the knowledge that their loved one is receiving an effective treatment reduced that anxiety significantly. This also improved relationships overall. The majority of patients reported that they were able to resume normal day-to-day tasks, self care and their usual activities again, which reduced the impact of their CLL on family and friends. **Patients said:** "my wife is smiling again knowing I have this treatment and seeing how well I am now" "My husband has been able to return to work as I no longer need his help" "Our dignity is restored as we have been able to come off benefits and no longer need paid carers" "we had a happy family Christmas without the worry of my CLL"

	When asked about their experience and their long-term health and well-being patients reported as follows: “no side effects whatsoever” “hardly any side effects” “I have my life back” "I no longer feel like 'just a CLL patient' but a person again " "I've had a holiday for the first time in years" "I feel so well that I've been able to go back to work" “Very benign experience”
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients will need some care in hospital in the early stages of Venetoclax treatment to ensure any possible tumour lysis syndrome is treated appropriately but patients are willing to accept this because of the potential benefits of the treatment. Attending hospital for the Obinutuzumab infusions could be more difficult for some patients. Infusion reactions are reported to be more common with Obinutuzumab than other monoclonal antibodies but that does not appear to be considered to be a disadvantage by patients. Patients in our survey did not report any unmanageable or significant side effects that would deter them from this treatment option. **Patients said:** Some fatigue from step-wise dose increases” “Some slight nausea early-on with indigestion/gas/diarrhoea which has improved significantly.” ‘My neutrophils dipped but soon recovered again”

	"The antibody infusions took a bit of time because I had a slight reaction. However, everything went smoothly after that"
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Because of the heterogeneous nature of CLL and the diverse population, with and without co-morbidities, who require an effective treatment, it is difficult to identify one population that would benefit more than others.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We would prefer this treatment to be available to all CLL patients receiving their first treatment.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Access to multiple treatment options is important as CLL is a heterogeneous disease affecting a wide range of patients.
- Venetoclax + Obinutuzumab is an effective, time limited treatment that induces deep remissions
- Venetoclax + Obinutuzumab offers a very acceptable safety profile to patients
- Venetoclax + Obinutuzumab should be available to all patients for their first treatment and would be more cost effective than Ibrutinib.
-

Thank you for your time.

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Patient organisation submission

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is a national blood cancer charity, first registered with the Charity Commission in 1969. We work to ensure that everybody affected by blood cancer has access to the right information, advice and support. Key services fall into 4 categories; • Patient services: such as a freephone helpline, nurse advisors, conferences and information booklets • Advocacy: individual advocacy, health technology appraisals, information and patient surveys • Campaigns: our biggest campaign is Spot Leukaemia, aiming to raise awareness of the signs and symptoms of leukaemia • Services for healthcare professionals, including conferences and online learning platforms. In 2016/17 and 2017/18, over 85% of our funding came from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, which in total represent approximately 15% of our annual income. Any funds received from the pharmaceutical industry are in accordance with the ABPI Code of Practice and the Leukaemia Care Code of Practice, our voluntary commitment that governs how we work with, and accept funding from, the pharmaceutical industry: www.leukaemiacare.org.uk/resources/code-of-practice
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	Financial year 18/19: Gilead: Support of our nurse conferences, £1250 Janssen-Cilag: Ad boards, £2050. Grants, £64,615. Support of our nurse conferences, £750.

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information primarily gathered through Leukaemia Care patient experience survey – 'Living with Leukaemia' (www.leukaemiacare.org.uk/living-with-leukaemia). The latest survey, run in 2017, had 2884 responses (including 1152 CLL patients). We have also recently started a patient advisory panel, where we hold focus groups to gather in depth information on patient experiences. This information supplements our quantitative survey data; we recently conducted a focus group with our CLL advisory panel, the results from which were presented at the recent iwCLL2019 meeting. Additionally, we have gathered information through our online forums, helpline, support groups, communication with our membership and one to one discussion with patients. We also work closely with other patient groups and share expertise.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia, with approximately 3,200 people diagnosed in England and Wales each year; however, it is still a rare condition. 85% of patients diagnosed aged 65 or older. CLL is also a heterogeneous condition, so the experience will be very different for each patient; therefore, a range of treatment options that fit individual needs as closely as possible is important. Common symptoms reported at diagnosis include fatigue (43% of those surveyed), swollen lymph nodes (32%) and fever or night sweats (27%). Patients with CLL also have a higher risk of infection, as their immune system is compromised by the disease. These frequent and persistent infections can impact hugely on quality of life, as well as being a leading cause of death for CLL patients. Additionally, current treatments can either cause side effects that last for a long time after treatment, or have to endure side effects for a long period of time whilst on a continuous therapy. Patients report that it is not just the severity of a side effect at the start of treatment that is concerning, it is also the time they must endure it for that is important. In addition to physical symptoms, being diagnosed with CLL has an emotional impact. In our survey, 38% of CLL patients said they felt more anxious or depressed since diagnosis. A 2016 survey conducted by the Chronic Lymphocytic Leukaemia Support Association (CLLSA) and the Canadian CLL Patient Advocacy Group (CLLPAG) conducted a survey of their forum members, as well as 10 carers. They found that CLL can also cause “stress” (75.8%), “anxiety” (59.3%), “difficulty sleeping” (38.7%) and “depression” (30.6%). This emotional impact is unsurprising given the course of the disease; CLL tends to respond less well to each line of therapy, with shorter subsequent remissions, leaving patients in fear of relapse. CLL patients would be reassured if there were treatments giving long and durable remissions from the start. As outlined above, living with CLL is difficult and does not affect a patient in isolation, but instead creates a “ripple effect” impacting on the whole family. Family, friends and colleagues of a patient may all be affected by the diagnosis. Family members/carers can be challenged with exhausting caretaking duties when someone they know is diagnosed with CLL. Even if CLL patients feel well and have few side effects day to day, patients report having to depend on their families more than they otherwise would and needing support unexpectedly. CLL patients are at increased risk of infection during treatment, due to a weakened immune system as side effect of the treatments. This presents a constant risk of hospitalisation, as the lack of immune system can lead to severe infections developing quickly.

	"I had a call to the helpline at midnight, during my FCR, which resulted in me having to drive into Manchester. I couldn't have driven so that's support from family and partner was critical then." – focus group participant "I've not got a partner to take me in, but I've got my two sons. If you were on your own, I don't quite know how you would cope to be honest with you." – focus group participant In the CLLSA/Canada CLLPAG 2016 survey, 18 out of 20 carers cited having to wholly take on previously shared household duties like meal preparation, shopping and upkeep of the household. This had led to many having to abandon their own jobs to be able cope with this increased burden, ultimately adding to the financial impact that living with CLL can cause. For some, caregiving was also cited as having direct physical health implications on the carer themselves. For a few, marital relations with their partners had ceased. Access to an effective treatment could release both the patient and carer to become contributors again, returning to the workplace, normal activities, and education again.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are 3 broad categories of first-line treatment available to the CLL patient and their clinicians. The current standard of care option for most (BSH guidelines 2018) is still chemotherapy based, such as the chemoimmunotherapy combination of fludarabine, cyclophosphamide and rituximab (FCR). However, FCR, as with most chemotherapy for other cancers, comes with many side effects due to its non-specific mechanism of action in the body. However, patients are keen to see treatments that work, but also favour those with better side effect profiles, seeing the two as a balancing act. In our survey, although improved survival/response is the most popular feature of a potential new treatment (indicated as important by 76% of patients), improved quality of life and tolerable side effects are also indicated as important by the majority (chosen by 68% and 56% of patients respectively). Further exploration with a CLL focus group suggests that whether more side effects are acceptable varies by person, by the type of side effects and also how long the effect lasts; more severe but for a shorter time might seem more reasonable. This is important as a large proportion of patients are unable to continue taking continuous therapies by the 5-year mark 50% of patients may have to discontinue a continuous therapy due to long term side effects, long term toxicity or because they have become refractory to the treatment. "There's no pain no gain… but there's a limit to the pain" – focus group participant

	For those who cannot tolerate FCR, due to age or comorbidities, other chemoimmunotherapeutic (CIT) options include bendamustine and rituximab, or chlorambucil combinations. However, these have been shown to be inferior to both FCR and newer treatment options, yet still come with the side effects of non-targeted treatments. Another important subset of patients not eligible for CIT are those with TP53 mutations or a 17p chromosome deletion. These mutations mean that CIT options do not work as well as it does in those without these genetic mutations. CIT has therefore been judged by the clinical community as unsuitable for high genetic risk patients, and that CIT does not work well enough to justify the harms caused by the chemotherapy. Treatment for these patients include ibrutinib, or idelalisib plus rituximab if they are unsuitable for starting ibrutinib. These patients have already lost the opportunity to use the first-choice option, which can cause distress to patients due to CLL being incurable but relapse/remitting. This difficult to treat population require more effective options and a treatment of a fixed duration that offers a chance at achieving a durable remission and treatment free period.
8. Is there an unmet need for patients with this condition?	There are unmet patient needs across all potential subgroups and all deserve ventoclax plus obinutuzimab to be an option for them. As mentioned above, the current standard of care for treating fit patients is FCR. Whilst this is effective for that group, can achieve enduring remission and was step change in management when it was proposed as a combination, downsides such as its side effects are not favoured by patients. CIT also comes with a risk of significant long-term side effects, such as continued cytopenias, MDS or second cancer development. Venetoclax and obinutuzumab offers these patients the chance to have non-chemoimmunotherapeutic, more tolerable option that is delivered over a limited time period. For less fit patients, such as those that are frail or older, other CIT options are available where FCR cannot be used but are not as effective as FCR. Leukaemia Care's report "I wasn't born yesterday" highlights, using case studies and survey data, that the majority of older patients still want treatments to be as effective as possible in prolonging their life or keeping their disease in remission. Side effect profile becomes more important to them when deciding on treatment, but efficacy is also really important. Therefore, they need a more efficacious option than non-FCR or BR CIT. Patients with comorbidities are a population in need of effective treatments with fewer side effects, as they may already be debilitated in some way by those comorbidities and find it harder to cope with added ill effects. There are also specific comorbidities that can be made more serious by certain treatments, such as heart conditions with ibrutinib. This highlights the need for a range of effective treatment options to suit different needs. As mentioned previously, a patient's genetic status affects the number of treatment options available to them. Whilst new treatments have been approved for those with TP53 mutations or 17p deletions, they are not suitable for

	all, with problems due to comorbidities. Also, not all patients are in favour of continuous therapies (see advantages below), but continuous therapy is the only option currently for those not suitable for CIT. The IGHV mutation status of a patient, another type of genetic mutation, are also not taken account of in current NICE guidelines for treatment options, despite being included in criteria to help clinicians ascertain best treatment options with patients (iwCLL 2019). Patients with unmutated IGHV genes are less likely to respond well to FCR and so require new effective treatment options. Unlike TP53/17p status, there are no treatments specially approved for IGHV unmutated patients. Both unmutated and mutated patients would benefit from access to an effective treatment option of a limited duration that offers a more attractive side effect profile and chance at achieving an enduring remission.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is well recognised that enduring remission can be obtained and can be indicated by the speed and depth of MRD negativity. There is evidence from the CLL14 trial that patients are achieving this deep MRD negativity when treated with venetoclax and obinutuzumab, increasing the likelihood of enduring remission. This is a positive for patients; they are likely to have fewer symptoms in remission and then be more likely to be able to return to work, for example. CLL patients recognise that MRD negative is a positive result in terms of the efficacy of treatment. Some would even suggest that they would consider it to be cured, if they were able to maintain the response. "Q: How do you define cure, in CLL? A: Oh gosh, MRD negative for a very long… you just never come out of MRD negative I suppose." – focus group patient The idea of representing a cure might not be corroborated by scientific evidence at present, but it does demonstrate patient desire to reach a state of remission that lasts as long as possible. Venetoclax and obinutuzumab is designed to be given for 12 months, followed by a treatment free period. Our survey shows that 64% of CLL patients would consider this treatment-free period as a positive. Whilst CIT treatments also allow a treatment free period, venetoclax and obinutuzumab are more efficacious and have more tolerable side effects.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients are aware of the risk of tumour lysis syndrome (TLS), as it is linked to the efficacy of the treatment. However, the dosing schedule in guideline has minimised the risk. Patients are happy with this TLS as a risk when balanced with the efficacy of the treatment.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All patients would benefit and need access to effective options. It is difficult to pick one above the other all have limited options.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are potential equality issues if only frail patients, those likely to be older, were to get access alone; all CLL patients are classed as disabled under the Equality Act, and should therefore be treated equally. Younger patients deserve equal access to and choice of treatments as much as older ones.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Multiple treatment options are required to effectively treat CLL over time as the disease cycles between treatment and active monitoring over time; being able to achieve a deep and enduring remission at first treatment would be reassuring for patients.
- Downsides of current treatments include long term side effects, including a risk of secondary cancers, and the high rate of patients discontinuing, due to toxicity or relapse, with therapies that must be taken continuously.
- The CLL patient population is extremely heterogenous, yet venetoclax plus obinutuzumab should be available as a first line treatment option for all patients as all these different patients have unmet needs that this treatment could address.
- Venetoclax plus obinutzuzimab is a treatment of a limited duration, offering durable remissions and a treatment free period; these are seen as favourable attributes of treatment options by patients.
- Venetoclax plus obinutuzimab offers patients a treatment option with a more favourable side effect and safety profile.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Lymphoma Action **Note that we support the submission made by CLL Support Association, prepared in collaboration with Lymphoma Action**
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity registered in England and Wales and in Scotland (see www.lymphoma-action.org.uk). Our primary aim and objective is to provide information, advice, support and training to everyone affected by lymphoma. We work throughout the UK, publishing leading, quality-assured written information on lymphoma, operating a clinical trials information service (Lymphoma TrialsLink at www.lymphomas.org.uk/lymphoma-trialslink) and providing a national helpline, a network of support groups and a buddy scheme. We have launched a well-being programme specifically designed for those with lymphoma (Live Your Life). We also provide education and training courses for healthcare professionals, as part of their CPD. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. Lymphoma Action is not a membership organisation.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	AbbVie(venetoclax): £10,000 –sponsorship of education and training/survivorship events; publications; core services Roche (obinutuzumab): £20,000 –sponsorship of education and training/survivorship events; publications; core services Gilead Sciences (idelalisib): £38, 000 –sponsorship of education and training/survivorship events; publications; core services Janssen-Cilag (ibrutinib): £15,000 –sponsorship of education and training/survivorship events; publications; core services

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Via collaboration with CLL Support Association**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	See CLLSA submission

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	See CLLSA submission
8. Is there an unmet need for patients with this condition?	See CLLSA submission
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	See CLLSA submission
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	See CLLSA submission

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	See CLLSA submission
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	See CLLSA submission

Other issues	
13. Are there any other issues that you would like the committee to consider?	See CLLSA submission

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- We support the submission made by the CLL Support Association, prepared in collaboration with Lymphoma Action
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	RCPath /BSH/ UK CLL FORUM

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	X☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? X☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKCLL Forum is an umbrella organisation for CLL in the UK which aims to bridge the gap between the clinical and scientific aspects of the disease, encourages collaborative research and promotes education of healthcare professionals and patients. It provides a framework where the UK CLL community, can provide input towards national guidelines, good clinical practice and translational science. The forum facilitates communication between healthcare providers, patients and funding bodies. UK CLL Forum is a charity organisation and does receive support from interested Pharma companies. The British Society for Haematology (BSH) is the largest UK haematology organisation . Members work together to share ideas and knowledge, and to champion and strengthen haematology practice. It provides access to resources, events and education that support professional development, bridges the gap between research and practice, and produces guidelines to raise the standards of clinical and patient care. The Royal College of Pathologists is a professional membership organisation, whose mission is to maintain the internationally renowned standards and reputation of British pathology, through training, assessments, examinations and professional development, for the benefit of the public. It is a registered charity and is not a trade union.

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes for CLL Forum: AbbVie paid the UK CLL Forum in the last 12 months £13,000: £8000 on 4/3/2019 for the sponsorship of the Annual Educational Scientific Day and on 2/11/2018 £5000 for the 2018 Clinical Sciences Educational Day; other payments Payment received for these in the last 12 months were: Gilead £10,000 (20/02/19); Janssen £7000 (08/03/19 and 01/09/2019) Roche £10,000 (02/05/19)
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	CLL is currently considered an incurable cancer. It is a disease characterised by uncontrolled proliferation of lymphocytes within the bone marrow and/or lymph nodes. This leads to progressive bone marrow failure and/or worsening lymphadenopathy. The aim of treatment is to induce remission by clearing disease within

mobility, to cure the condition, or prevent progression or disability.)	the bone marrow and nodes with minimal toxicity in order to improve quality of life, progression free and overall survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In addition to resolution of lymphadenopathy and bone marrow function, we now can now also look for very deep remissions in the blood and bone marrow, using high resolution flow cytometry or next generation sequencing to detect low levels of CLL (Minimal Residual Disease or MRD). We know that in the context of treatments such as chemoimmunotherapy (CIT) and novel agents like Venetoclax, deeper remissions translate into improved PFS and even OS.[1-3]
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. First line CLL patients (irrespective of age) who have unmutated immunoglobulin heavy chain genes (IGHV) are a clear patient group with unmet need as they have poor progression free and overall survival when treated with chemoimmunotherapy (CIT). CIT is currently the cornerstone of frontline treatment for CLL patients with intact TP53 (no mutation or deletion) on the NHS. Yet it has been demonstrated in multiple studies that unmutated IGHV predict for an inferior PFS and OS in the context of CIT for CLL patients. [4,5]. Randomised controlled trials have now demonstrated that Ibrutinib is superior to CIT in terms of PFS in the frontline setting when compared to three standard frontline CIT regimens - FCR[6], BR[7] and Chl+O [8]. There was also an OS benefit seen with Ibrutinib in comparison to FCR. Importantly all three studies report that patients treated with Ibrutinib show no difference in PFS outcomes between IGHV unmutated and mutated CLL patients, in contrast with CIT-treated patients where IGHV unmutated patients have a consistently worse outcome than IGHV mutated patients. Ibrutinib is not

	currently funded in the frontline setting for TP53 intact CLL and access is currently restricted to frontline treatment of TP53 mutated/ deleted CLL. The highest unmet need is therefore in all CLL patients with intact TP53 but unmutated immunoglobulin genes, irrespective of age. There is also a need to reduce toxicity of currently available CIT treatments for all CLL patients with intact TP53 in order to improve quality of life while maintaining depths of remissions. Even in patients with TP53 mutated/deleted CLL, while Ibrutinib is a very effective therapy, it is a continuous treatment and toxicities such as infections, atrial fibrillation and arthralgia can significantly impact on the quality of life of patients particularly those with pre-existing co-morbidities. If we can deliver more effective, less toxic therapy and induce deeper remissions in CLL patients, the majority of whom are elderly, we will reduce hospital admissions and improve both quantity and quality of life. CLL treatment has significant impact on patients ability to work: the Leukaemia Care 'Living with Leukaemia' survey reports that 43% of CLL patients had a temporary impact during treatment and 57% permanent.[9] If PFS is significantly prolonged we will reduce the number of patients who progress and require further therapy.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In the frontline setting patients with intact TP53 are treated with CIT– FCR is the current standard for fit patients while Chlorambucil in combination with Obinutuzumab is used for less fit patients or those with co-morbidities. Patients with mutated/deleted TP53 CLL are treated with Ibrutinib in the frontline setting or with single agent Venetoclax if a B-cell receptor pathway inhibitor is unsuitable. Idelalisib with Rituximab is also available for patients in this scenario. Currently Ibrutinib, Idelalisib and single agent Venetoclax are administered continuously until there is unacceptable toxicity or disease progression.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	1. BCSH guidelines [10]; these are already out of date 2. iwCLL guidelines [11]
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes the pathway is reasonably well defined based on the accessibility of drugs on the NHS. Currently patients with intact TP53 will be treated with either FCR CIT or entered into the FLAIR trial for frontline therapy. Older patients or those not fit for FCR due to co-morbidities are treated currently with, Bendamustine and Rituximab or NICE approved Chlorambucil and Obinutuzumab. Patients with CLL harbouring a TP53 deletion or mutation are currently eligible for Ibrutinib in the frontline setting.
• What impact would the technology have on the current pathway of care?	The randomised controlled CLL14 trial evaluated time-limited Venetoclax+Obinutuzumab (Ven+O) for 12 months against Chlorambucil+Obinutuzumab (Chl+O) in in a population that was representative of the vast majority of patients seen in clinical practice. The median age of patients on the study was 72 years.[12] CLL patient needing treatment can be broadly divided into the categories as below- 1. <u>Less fit or elderly patients–</u> These patients currently receive Chl+O. The CLL14 study demonstrated a significant improvement in PFS with Ven+O of 88% compared to 64% with Chl+O at 2 years.The rate of minimal residual disease (MRD) clearance in peripheral blood was more than twice in Ven+O arm compared to the Chl+O arm – 75% vs 35%. As previously highlighted, MRD negative remissions predict for longer, symptom free remissions and longer time to next treatment. In the elderly population this is likely to mean fewer patients ever needing next line Ibrutinib. The trial also confirms that Chl+O shows inferior outcomes for patients with unmutated IGHV CLL (approx 50% PFS at 2 years). In contrast, Ven+O was equally effective in both mutated and unmutated CLL patients.

	In summary this technology will lead to improved PFS in all patients, but especially those with unmutated IGHV genes. 2. Fit patients – The current standard of care is NICE approved FCR. Outcomes with FCR are inferior for patients with unmutated IGHV genes, but in the UK we have no alternative therapy available to deliver despite excellent evidence of benefit from novel therapies. PFS and OS benefit have been demonstrated with continuous therapy with the B-cell receptor Ibrutinib when compared to FCR. Ibrutinib was equally effective in CLL with both mutated and unmutated IGHV in this study.[6] Ven+O provides an excellent, time limited alternative to Ibrutinib in this younger patient cohort. There will not be a clinical trial comparing Ven+O to FCR. Although the CLL 14 study recruited older and frailer patients, there is no reason to doubt that Ven+O will provide the same benefits in a younger cohort. Given the greater toxicity of FCR both in the short term with hospital admissions and in the longer term with immunosuppression and risk of second malignancies, it is important that Ven+O should be available as a superior therapy for younger patients with unmutated IGHV genes, and ideally as a choice for all. 3. All CLL patients withTP53 mutation or deletion – The current standard of care for these patients is Ibrutinib which is NICE approved. While this is a very effective treatment option it is administered on a continuous basis until progression or unacceptable toxicity. It is becoming clear with longer follow up that there is a continuous pattern of relapse in Ibrutinib treated patients with a significant proportion discontinuing treatment due to toxicity.[13] Idelalisib, an alternative BCRi is not currently recommended for frontline treatment of CLL due to its toxicity profile in this setting, Ven+O therefore represents a valuable, time-limited option in these patients.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See above
• How does healthcare resource use differ between the technology and current care?	Both current and new technologies are using intravenous antibodies. VenO is delivered for the fixed duration of 12 months..
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Haematology Units as specified in nice.org.uk/guidance/ng47
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes

• Do you expect the technology to increase length of life more than current care?	Yes, significantly
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, significantly
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	All CLL patients who need treatment as per iwCLL guidelines[14] should be offered this treatment option based on arguments discussed above
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Only high risk patient will require brief hospitalisation for tumour lysis assessment and prophylaxis; other risk groups can be managed in day-case units. Ven O treatment is limited to 12 months. Venetoclax monotherapy was shown to have improved health related quality of life in patients who failed treatment with Ibrutinib of Idelalisib. [15].

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	IGHV and TP53 analysis, these assessments are already recommended in the existing guidelines
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There will be substantially reduce number of patients who will relapse and require further treatment, significant proportion will be probably cured of CLL (judging on 51% of patients reaching MRD of 10^{-6})

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	see above Treatment with Ibrutinib in relapsed patients has shown significant improvement not only in disease control, prolonging survival but also in restoring quality of life.[16] VenO is likely to deliver similar outcome but with limited duration treatment.
• Is the technology a 'step-change' in the management of the condition?	Yes,
• Does the use of the technology address any particular unmet need of the patient population?	Ibrutinib and Idelalisib have improved survival in TP53 deleted/mutated patients, however this treatment does not lead to MRD negative disease, side effects profile is significant, patients must have antibiotic prophylaxis and finally majority of patients will relapse after 5 years of treatment [17], longer for patients treated with ibrutinib front line (<10% progress in 4 years)[6]; therefore limited treatment to 12 months of Ven O is preferable for costs and also patient participating in Leukaemia care survey >60% patients prefer limited time treatement.[18]
17. How do any side effects or adverse effects of the	Once 5 weeks of titration is completed the rest of the treatment is easy to administer and well tolerated by patients.

technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and MRD, both were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, EMA approved
• Are there any adverse effects that were not	No

apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real world evidence [19] Eyre, T.A., *et al.* Efficacy of Venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. *British journal of haematology* **185**, 656-669 (2019). [20] Mato, A.R., *et al.* A retrospective comparison of Venetoclax alone or in combination with an anti-CD20 monoclonal antibody in R/R CLL. *Blood advances* **3**, 1568-1573 (2019). [21] Roeker, L.E., *et al.* Tumor Lysis, Adverse Events, and Dose Adjustments in 297 Venetoclax-Treated CLL Patients in Routine Clinical Practice. *Clinical cancer research : an official journal of the American Association for Cancer Research* **25**, 4264-4270 (2019). [9]https://media.leukaemiacare.org.uk/wp-content/uploads/Living-with-Leukaemia-2018-Full-Report-Web-Version.pdf
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA174,	No

TA216, TA343, TA359, TA429]?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes CLL14 was designed for “frail” patients, however as argued in #9, this treatment should be offered to “fit“ patients as well.
22b. Consider whether these issues are different from issues with current care and why.	no
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- For the best outcomes the most effective treatment should be given first, novel therapies (BTK and BCL2 inhibitors) are clearly better than CIT in all patients groups;
- "Fit" and "unfit" patients' distinction is redundant in the era of novel therapies
- Young fit patients treated with CIT are suffering long term sequelae leading to significant health costs

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NCRI/RCP/RCR/ACP
3. Job title or position	RCP registrar
4. Are you (please tick all that	☒ an employee or representative of a healthcare professional organisation that represents clinicians?

apply):	☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI, UK government**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**NO**
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**

The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve progression free and overall survival of patients with CLL
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	PFS, OS and also absence of minimal residual disease as measured by either standardised flow cytometry or next generation sequencing.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With chemo-immunotherapy depending on fitness of patients: FCR for fit patients and Chlorambucil& Obinutuzumab (CHL-OBI) for frail patients and Ibrutinib for patients with deleted or mutated TP53

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSH guidelines: Schuh A et al BJH 2018; these are already out of date ESMO guidelines: Eichhorst et al iwCLL guidelines: Hallek M, Blood 2019
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined by NICE thanks to the approvals of FCR and CHL-Obi and Ibrutinib for patients with deleted or mutated TP53.
• What impact would the technology have on the current pathway of care?	Frail patient group, unmutated IGHV: Ven-Obi would have a huge impact thanks to the very significant improvement in PFS compared to Chl-Obi of 88% vs 64% at two years. This is also reflected in the MRD negativity rate of 75% vs 35% in the peripheral blood. We know that this measure can be a surrogate marker for PFS for the majority of current therapies, It means that more patients will obtain long lasting remissions and remain without the symptoms seen in CLL. It also means that fewer patients will require Ibrutinib at relapse as they will have died of other causes than CLL. Frail patient group, mutated IGHV: With a median follow-up of 29 months, this group of patients does as well as the unmutated group on Ven-Obi. However, there is no difference in PFS at two years compared to the Chl-Obi treated patients. We know from other studies that IgHV hypermutated patients with CLL do extremely well with CIT. We therefore suggest to give these patients the choice between CIT or Ven-Obi. In the CLL14 study, these patients made up 30% of the total population. This is a realistic proportion. Fit patients, unmutated IGHV: These patients are currently treated with FCR according to NICE recommendation. There has not been a study comparing Ven-Obi against FCR and this study will never happen. Three studies recently compared Ibrutinib +/- anti-CD20 with CIT. All three studies showed an inferior PFS with CIT and in one of the studies, fit patients treated with

	FCR had an inferior overall survival compared to Ibrutinib treated patients. When comparing across studies, FCR treated unmutated patients had a two years PFS of 75% against 88% from the CLL14 for Ven-Obi. MRD rates were 59% versus 75% suggesting at least non-inferior efficacy for Ven-Obi. Importantly, Ven-Obi has a very superior safety profile compared to FCR without the 25% risk of hospital admissions seen with FCR and no evidence for long-term sequelae such as secondary bone marrow failure (MDS) or second cancers associated with the use of chemotherapy agents. This is particularly important in the younger patients. Fit patients, mutated IgHV: There is similar efficacy of Ven-Obi and FCR in this patient group at the 2 year timepoint. Besides, with longer follow-up of CIT treated patients, we know that these do exceedingly well with CIT if there are no major side-effects from FCR. We would therefore suggest to give patients the choice between FCR and Ven-Obi. TP53 deleted/mutated patients irrespective of fitness and IGHV status: For this subgroup of patients (10-12% of all patients with CLL needing treatment), ibrutinib is already NICE approved. However, about 25% of patients stop ibrutinib (at 2 years) mainly for intolerance/toxicity and all are projected to discontinue it over time of treatment. For these patients, we currently have limited treatment options. Idelalisib has a role in the treatment of ibrutinib-intolerant TP53 disrupted CLL; however, idelalisib also has significant side-effects and few patients stay on drug for longer than 12 months. Importantly, ibrutinib is given continuously whereas Ven-Ob is given for 12 months only. We therefore advise to allow patients to choose between Ibrutinib and Ven-Obi.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	See above
• How does healthcare resource use differ between the technology and current care?	Both current and new technologies are using intravenous antibodies. The fixed duration treatment of Ven-Obi is a huge advantage for the 10-12% of patients currently receiving continuous Ibrutinib.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist haematology centres only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
• Do you expect the technology to increase length of life more than current care?	yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Specific groups that will benefit in addition to the frail patient group of CLL14: IgHV unmutated; TP53 deleted/mutated, fit patients
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	For TP53 wild-type patients: Easier to use as much better tolerated than CIT (FCR; Chl-Obi). However, due to the initial dose escalation phase of venetoclax, there is a need for hospitalisation to monitor tumourilysis (TLS) in a small proportion of patients. For TP53 disrupted patients: No need for continuous therapy with ibrutinib, but Ven-Obi includes an intravenous antibody Similar needs for co-medication, but a short-term need over 5 weeks for prophylaxis of TLS on Ven-Obi that is dependent on the TLS risk assessment. Need to test for IgHV mutation status
14. Will any rules (informal or formal) be used to start or stop	IGHV mutation status

treatment with the technology? Do these include any additional testing?	TP53 mutation analysis
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The main advantage of this technology is its tolerability, but there is a need for close surveillance for 5 weeks because of the risk of TLS.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, it is likely that a significant number of the MRD negative patients are cured. For example, 51% of patients treated with Ven-Obi were in a deep molecular MRD at 10^-6 by sequencing.
• Is the technology a 'step-change' in the management of the condition?	Yes, thanks to its tolerability and high MRD and PFS results
• Does the use of the technology address any particular unmet need of	TP53 disrupted CLL remains a challenging condition. So far, we only had ibrutinib or idelalisib. While these drugs are much more effective than chemotherapy, they have side-effects and the presence of TP53 mutation/deletion still

the patient population?	means that patients respond less well and relapse sooner than patients with standard risk CLL. It is therefore important to increase the therapy choice for this patient group.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	See above: this is mainly the management of TLS
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFs and MRD, both were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical	Yes, EMA approved

outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real world evidence: Eyre, T et al Br J Haematol. 2019 May;185(4):656-669. Roeker LE et al: Clin Cancer Res. 2019 Jul 15;25(14):4264-4270 Mato AR et al Blood Adv. 2019 May 28;3(10):1568-1573
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA174, TA216, TA343, TA359, TA429]?	No
21. How do data on real-world experience compare with the trial	There is no frontline RWE for Ven-Obi. However, side effect profiles of patients treated with Venetoclax for relapsed CLL outside of clinical trials are comparable to the trial evidence.

data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Definitely. The CLL14 study included only frail patients and CIRS scores of >6 and Creat Clearance of less than 70mls/min. Clearly, fit patients should also be given the choice to have this hugely superior treatment that is better tolerated than any other therapy. These make up approx. 25% of our CLL community in the UK requiring therapy.
22b. Consider whether these issues are different from issues with current care and why.	no
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Ven-Obi is superior to CIT with respect to ORR, PFS and MRD negativity across all subgroups.
- Ven-Obi is far better tolerated than CIT across all subgroups.
- It would be unethical to deprive fit patients from access to Ven-Obi when it has shown to be hugely beneficial for unfit, frailer patients.
- Compared to CIT, the benefit of Ven-Obi for patients with hypermutated IgHV locus with respect to PFS is less obvious and longer follow-up is needed. However, Ven-Obi is better tolerated. Ideally, these patients should therefore be given the choice.
- For patients with TP53 disruption, Ven-Obi should become another option alongside ibrutinib that is already NICE approved as Ven-Obi is at least as effective and certainly better tolerated.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Anna Schuh**
2. Name of organisation	**University of Oxford**
3. Job title or position	**Consultant Haematologist**

4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? x☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐x yes, I wrote the submission document on behalf of the RCP I would like to add that since the submission of the RCP document, the NCRI CLL study group has finalised the design of the next national NCRI frontline Phase 3 trial called ERASE CLL. ERASE CLL is expected to recruit 732 patients with newly diagnosed CLL over 3 years. This study is based on the assumption that there will be NHS supply of Ven-Obi as the standard-of-care control arm for a 1:4 randomisation. This means that 586 patients will be recruited into the experimental pharma-funded treatment arm saving the NHS significant treatment costs. Negotiations with our pharma partner are ongoing, but ultimately their successful outcome depends on having the control arm Ven-Obi available as the standard of care in the NHS.
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the	

condition, or prevent progression or disability.)	
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	

• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related	

quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator	

treatments since the publication of NICE technology appraisal guidance TA343 and TA429?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab	

(FCR) and bendamustine with or without rituximab (BR) are unsuitable. How is this FCR/BR-unsuitable population clinically defined? 25. Is chlorambucil with or without rituximab (excluded as a comparator in the company submission) considered to be established clinical practice in the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable?	

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

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Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

[Insert appraisal title here]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Jackie Martin**
2. Are you (please tick all that apply):	**x** a patient with the condition? ☐ a carer of a patient with the condition? x a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Joint nomination from Chronic Lymphocytic Leukaemia Support (CLL Support) and Lymphoma Action (LA)
4. Did your nominating organisation submit a submission?	**x** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x** yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and	

care available on the NHS?	
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and	

explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Topic-specific questions	
16. The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) and bendamustine with or without	

rituximab (BR) are unsuitable. How is this FCR/BR-unsuitable population defined? 17. Is chlorambucil with or without rituximab (excluded as a comparator in the company submission) considered to be established clinical practice in the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable?	

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

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-
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-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nick York**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Leukaemia Care
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: I have advocated for CLL patients as a volunteer and trustee of patient groups for 5 years and work today in an employed post as a patient advocate which includes 7 years HTA support experience. I was treated 1st Line with FCR, very short remission and high level of side effects experienced. ☒ I am drawing on others' experiences. Please specify how this information was gathered: experiences gained through administrating patient forums, support groups and meetings for 7 years. Also, from focus group discussions and patient experience surveys carried out by Leukaemia Care.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The uncertainty and long-term complications caused by disease progression and treatment toxicities means that negative quality of life is a constant burden: before, during and between treatments. The reducing efficacy of future treatments following eventual 1st relapse adds to this burden, with many succumbing to infectious complications. We live in fear of relapse and reducing access to effective treatments, this impacts negatively on family and friends too (carers). With many patients unable to carry out normal duties of daily living, the burden and added stress alongside the financial burden on the family falls on to the carer's shoulders. To describe the disease in short; I could say that I find living with the

	disease 'tiring and debilitating, hard to adjust to and emotionally challenging'. This is caused by constant bouts of fatigue, having to navigate frequent infection, continuous treatment, managing prophylaxis and immunoglobin supplementation, reduced social interaction, reduced ability to carry out normal activities, long periods of feeling unwell, fear of long-term complications and eventual death.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Due to the heterogeneity of this disease and variety of patient needs, currently available treatment options do not offer patients equal opportunities to effective or tolerable treatments. Patients and treating physicians require more choice and access to effective therapies.
10. Is there an unmet need for patients with this condition?	Many patients must accept less effective therapy due to age and comorbidities or must accept treatment using strong immunochemotherapeutic regimens and the long-term consequence of further compromising their immunity, a reduced quality of life, side effects and risk of second cancers. Indeed, the population with mutated IGHV may gain most benefit from use of strong chemo immunotherapies 1st line, however those with unmutated my not fare so well. Options are required to stratify patient treatment by clinical suitability, personal preference of treatments and lifestyle consequence. In the age of effective non-chemotherapy-based combination treatments of a fixed duration, venetoclax plus obinutuzimab offers all patients an effective therapy with a more tolerable side effect profile. As important is that; this is a treatment of a fixed duration, so it offers a chance of achieving an enduring remission and treatment free remission to all, including those living with an 17p aberration and the challenges of continuous therapy.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This is a step change in how CLL can be treated enabling the chance of all patients to consider long term treatment plans and potential management of their disease. As above, venetoclax plus obinutuzimab offers all patients a chance/choice of an alternative of an effective 1st line therapy without chemotherapeutic related complications, offering all including those unsuitable for strong chemotherapy a chance of achieving an enduring 1st remission and treatment free period, an improved quality of life and

	ability to resume tasks of normal daily living and become contributors again. Carers and family also carry an immense burden for their loved ones, often having to step in to carry out all family tasks at the expense of their own quality of life and incomes. A treatment with less toxic and side effect profile can help carers and patients.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Potential admission increased early protocol and costs associated during early dose escalation stages of treatment to reduce TLS risk. However, patients understand that this is due to having to balance the effectiveness of the therapy and are willing to undertake this.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All patient groups will benefit from access to venetoclax plus obinutuzumab, which can offer all a chance of an enduring remission. In this new age of targeted combination therapy there should not be reliance on treatment paradigms that will cause discrimination of subgroups by selection of suitability based upon fitness and age.
Equality	
14. Are there any potential equality issues that should be taken into account when	CLL patients may live with one or other or both protected characteristics of age and disability. Access to a therapy that is effective and clinically suitable for all should not be restricted to the older frailer population when younger fitter patients would benefit equally.

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	As above
Topic-specific questions	
16. The company have focussed the submission on the CLL population for whom fludarabine, cyclophosphamide and rituximab (FCR) and bendamustine with or without rituximab (BR) are unsuitable. How is this FCR/BR-unsuitable population defined?	In the age of targeted combination therapies and venetoclax plus obinutuzimab that are effective in all groups. I do not believe that this treatment should be restricted to those unsuitable for FCR/BR. This therapy is as effective in the fit and unfit, Therefore I find it difficult to define suitability of one group alone.
17.	It is my understanding that chlorambucil alone or chlorambucil with rituximab may often be all that is suitable to the very frailest patients, effective alternative options should remain open to them.

Is chlorambucil with or without rituximab (excluded as a comparator in the company submission) considered to be established clinical practice in the NHS for treating people with CLL for whom fludarabine-based treatments are unsuitable?	

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

- CLL is a heterogenic condition and requires many treatments, venetoclax plus obinutuzimab is a step change in how CLL is treated, offering an effective therapeutic alternative to chemoimmunotherapy or continuous therapy.
- Use of venetoclax plus obinutuzimab should not be stratified by FCR/BR unsuitability, age or fitness. In the age of effective targeted combination therapies of a limited duration, they may be clinically suitable for all.
- Restricting an effective option to a predominantly older frail population is negatively discriminating against younger cancer patients
- Venetoclax plus obinutzuzimab is a fixed duration therapy which offers all patients a chance at achieving a durable remission and treatment free period.
- Venetoclax plus obinutuzimab has a more tolerable and reduced side effect profile than chemoimmunotherapy

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia ID1402

Produced by: Warwick Evidence

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Daniel Gallacher (Research Fellow) reviewed and critiqued the statistical analysis and undertook additional analyses; Lazaros Andronis (Associate Professor) and Mandana Zanganeh (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) and Emma Loveman (Senior Researcher) reviewed and critiqued the clinical effectiveness evidence; Samantha Johnson (Information Specialist) critiqued the company searches and undertook additional searches; Anna Brown (Information Specialist) provided additional information specialist support; Scott Marshall (Consultant Haematologist) provided expert clinical advice; Daniel Todkill (Clinical Research Fellow) provided clinical advice; and Hema Mistry (Associate Professor) co-ordinated the project and the report, and reviewed the draft and final reports.

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Glossary

AE	adverse event
AIC	Akaike information criteria
B-CLL	B-Cell Chronic Lymphocytic Leukemia
BIC	Bayesian information criteria
BNF	British National Formulary
BR	bendamustine and rituximab
BSH	British Society of Haematology
CDSR	Cochrane Database of Systematic Reviews
CEM	cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIRS	cumulative illness rating scale
Clb	chlorambucil
CLL	chronic lymphocytic leukaemia
COPD	chronic obstructive pulmonary disease
CrCI	creatinine clearance
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CS	company submission
CSR	clinical study report
del(17p)	deletion of the short arm of chromosome 17
DOR	duration of response
EFS	event-free survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	end of treatment assessment
EQ-5D-3L	EuroQol 5 dimensions
ERG	Evidence Review Group
ECOG	Eastern Cooperative Oncology Group
FCR	fludarabine, cyclophosphamide and rituximab
FTD	fixed treatment duration
GClb	chlorambucil and obinutuzumab
HR	hazard ratio
HRQoL	health-related quality of life
HSUV	health state utility value
ICER	incremental cost-effectiveness ratio
IGHV	immunoglobulin heavy chain gene variable region
IRC	independent review committee
ITT	intention-to-treat
LYs	life years
KM	Kaplan-Meier
MAIC	matching adjusted indirect comparison
MDASI-CLL	M.D. Anderson Symptom Inventory-CLL
MRD	minimal residual disease
NE	not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
NR	not reported
ORR	overall response rate

OS	overall survival
PAS	patient access scheme
PD	progressive disease
PFS	progression free survival
PPS	post-progression survival
PR	partial response
PROs	patient reported outcome measures
PS	performance status
PSA	probabilistic sensitivity analysis
QALYs	quality-adjusted life years
QOL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SLR	systematic literature review
SPC	summary of product characteristics
TA	technology appraisals
TEAE	treatment-emergent adverse event
TOT	time on treatment
TONT	time on next treatment
TTE	time-to-event
TTNT	time to the next anti-leukemic treatment
TLS	tumour lysis syndrome
UK	United Kingdom
VenG	venetoclax with obinutuzumab
WTP	willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The National Institute for Health and Care Excellence (NICE) scope for this appraisal is the clinical and cost-effectiveness of venetoclax with obinutuzumab (VenG) within its marketing authorisation for untreated chronic lymphocytic leukaemia (CLL).

The population in the company's submission (CS) is people with untreated CLL with coexisting conditions that make fludarabine and bendamustine (FCR/BR) based therapy unsuitable. This is the population in the pivotal CLL14 trial and reflects the company's anticipated positioning of VenG in the National Health Service (NHS) treatment pathway. However, this population is narrower than the anticipated marketing authorisation and may not be wholly generalisable to the population that UK clinicians wish to use VenG for.

The CS considers two key subgroups: those without a del(17p) or TP53 mutation and those with a del(17p) or TP53 mutation. The algorithm for identifying the del(17p)/TP53 mutation subgroup differs between the clinical and cost-effectiveness sections, resulting in differing sample sizes. The rationale for using different algorithms is not adequately justified by the company, although it has little impact on the results.

The comparators in the NICE scope are considered for the two subgroups. The submission includes obinutuzumab plus chlorambucil (GClb) for those without a del(17p) or TP53 mutation and ibrutinib for those with a del(17p) or TP53 mutation. Other scoped comparators are excluded with justification, which the Evidence Review Group (ERG) agrees with.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company provided data to the ERG in the following four submissions:

- The original CS and clinical study report (CSR): data-cut August 2018 (28.1 months median follow-up)
- The clarification responses and CSR Corrigendum: data-cut August 2018, correcting errors in the original CS Figure 15 for subgroup analysis of del(17p)/TP53 mutation
- The CS addendum and CSR supplement: data cut August 2019 (39.6 months median follow-up)
- The CS addendum clarification responses: data-cut August 2019

The CS presents evidence from one multi-centre randomised controlled trial (RCT) investigating the effectiveness and safety of VenG in people with previously untreated CLL with co-existing medical conditions. The comparator in the CLL14 trial was chlorambucil and obinutuzumab (GClb). Presence of coexisting conditions was defined by a total cumulative illness rating scale (CIRS) of >6 or creatinine clearance <70ml/min. The trial included 368 participants without del(17p)/TP53 mutation, 49 with del(17p)/TP53 mutation and 15 with missing data (clarification A4). Randomisation led to 216 participants in each treatment arm.

Follow-up of the CLL14 trial is ongoing and the CS addendum presents results from a data cut after a median of 39.6 months; when all participants had completed 12 cycles of treatment (August 2019). At this point, 177 participants remained in follow-up in the VenG arm and 178 in the GClb arm. The key outcomes are summarised below. Median progression free survival (PFS) or overall survival (OS) had not been reached in the VenG arm at the time of the analysis.

- Investigator assessed PFS (trial primary outcome) demonstrated superiority of VenG with a hazard ratio of 0.31 (95% confidence interval (CI) 0.22 to 0.44, p<0.0001). [redacted] deaths had occurred in each arm at the time of the latest follow-up. The hazard ratio for OS was 1.03 (95% CI 0.60 to 1.75, p=0.92), suggesting no difference between VenG and GClb, although there is a degree of uncertainty around the estimate.
- Response outcomes were assessed at end of treatment (3 months after a patient received their last treatment dose). A formal analysis of complete response (CR) and CR with incomplete bone marrow recovery (CRi) combined, demonstrated a difference in response rate of 26.4% in favour of VenG (95% CI 17.4% to 35.4%, p<0.0001).
- The stratified hazard ratio of duration of response (DOR), defined as the time from the first occurrence of a response until disease progression or death, was [redacted] (95% CI [redacted]) and separation of the Kaplan-Meier curves indicated a superior DOR in favour of VenG.
- Time to the next anti-leukemic treatment (TTNT) defined as the time between the date of randomisation and the date of a patient receiving a second line therapy or death also suggested that VenG has a significantly lower hazard rate of next treatment or death than GClb (stratified hazard ratio 0.51 (95% CI 0.34 to 0.78, p = 0.0012)). See discussion below regarding a potential interpretation issue with these data.

- The CS presents minimal residual disease (MRD) as a secondary trial outcome, although this was not a NICE scoped outcome. MRD was measured in both blood and bone marrow at various times during the trial. The main secondary outcome was rate of MRD negativity in blood at the 3 month post-treatment follow-up. The company reports that VenG achieved 75.5% MRD negativity compared to 35.2% in the GClb arm 3 months after treatment completion, but this reduced to 47.2% and 7.4%, respectively, 18 months after treatment completion or early termination. MRD negativity in bone marrow at 3 months post-treatment showed lower rates of negativity for both arms than the blood measurements (VenG 56.9%; GClb 17.1%), this was not measured 18 months after treatment completion.
- Health-related quality of life (HRQoL) was assessed with the EuroQol 5 dimensions [EQ-5D-3L]; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and symptoms were assessed with the M.D. Anderson Symptom Inventory-CLL [MDASI-CLL]. All showed a [redacted] from baseline score [redacted], but there were [redacted] between the arms of CLL14 at any point in the follow-up.
- The majority of participants experienced at least one treatment-emergent adverse event (TEAE); 14.6% and 15.9% of the VenG and GClb groups, respectively, discontinued a treatment for TEAEs. The most common Grade 3-4 adverse event was neutropenia, occurring in [redacted] (VenG) and [redacted] (GClb), respectively. Other common Grade 3-4 adverse events included thrombocytopenia, infusion related reaction and febrile neutropenia.
- In total [redacted]% of VenG participants and [redacted]% of GClb participants experienced at least one serious adverse event (SAE). The most frequently reported SAEs were febrile neutropenia, pneumonia, infusion-related reaction and pyrexia. In total [redacted]% (VenG) and [redacted]% (GClb) of participants had an adverse event that resulted in death.
- Tumour Lysis Syndrome (TLS) was reported in three VenG treated participants and in five GClb treated participants.

A naïve indirect comparison was made between CLL14 and three separate studies to compare VenG with ibrutinib for people with previously untreated CLL and del(17p)/TP53 mutation. The company's preferred study for this analysis was a retrospective cohort study of people with CLL treated with ibrutinib (Mato 2018). The study had a subgroup with del(17p) (n=110). Another study (Ahn 2018) was a single arm study of ibrutinib for CLL which reported a subgroup who were untreated and who had del(17p)/TP53 mutation (n=35); this indirect

comparison was undertaken as a sensitivity analysis in the CS. A comparison with ALLIANCE data was provided in clarification A23 and updated in the CS addendum.

- For the main comparison (Mato 2018), fitting a Cox proportional hazard model to the data produced a PFS hazard ratio of 0.660 (95% CI 0.270 to 1.615, p = 0.363). The confidence intervals are wide illustrating how uncertain the results are. Fitting another Cox model to the OS data produced a hazard ratio of 0.841 (95% CI 0.301 to 2.352, p=0.741). Again, the confidence intervals are wide.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The whole trial population of CLL14 is used as evidence for the subpopulation of people without del(17p)/TP53 mutation compared with GClb. This evidence includes a proportion of participants with del(17p)/TP53 mutation. The subgroup with del(17p)/TP53 mutation is compared via a naïve indirect comparison with ibrutinib monotherapy. The ERG notes therefore there is some double counting of participants.

The ERG generally agrees with the CS assessment that the trial has a low risk of bias for most domains, however we note the performance bias and detection bias inherent in an open label trial. We also consider that there is a risk of bias due to selective outcome reporting. In addition, although the arms are balanced with respect to key prognostic factors, there are some differences between groups in baseline comorbidities.

The details of, and reasons for, dose modifications of venetoclax, chlorambucil and obinutuzumab were not consistently reported in the CS.

The CS includes a non-scoped outcome, MRD rate. The ERG clinical advisor confirms that undetectable MRD is an important surrogate endpoint, particularly in bone marrow, and that there is a relationship between undetectable MRD and final outcomes in CLL, although recent evidence suggests the relationship between MRD and outcomes following venetoclax needs further validation.

The trial follow-up is ongoing and the data presented are from a data-cut that was not the originally planned primary analysis point. Data are therefore immature and it is not possible to draw conclusions for all of the specified outcomes.

The company does not present an analysis of whether the hazard ratio, which assumes proportionality of the hazard rates between the two trial arms, is a suitable outcome when reporting results of PFS. In the cost-effectiveness section, the company concludes that proportionality is not held and this would suggest that the estimate of the hazard ratio is not an accurate representation of the benefit of VenG on PFS. The ERG also notes that the analyses of DOR and event-free survival were performed without an assessment of proportional hazards. The analysis for OS was presented without a discussion of proportional hazards in the clinical effectiveness section but the assumption was investigated in the cost-effectiveness section of the CS.

It is unclear whether the inclusion of OS events introduces bias into the analysis of TTNT, as the company treats deaths as events in the TTNT analysis rather than as censored observations as stated in the original CLL14 trial protocol (though is consistent with later versions). The ERG therefore suggests caution in the interpretation of the TTNT results. Analysis of the TTNT outcome where death events were censored, provided in response to a request by the ERG, produced a hazard ratio of [redacted], but without confidence intervals or test of statistical significance (addendum clarification response).

Generalisability may be limited due to the restricted population reported in the evidence including only those with comorbidities in whom FCR/BR based therapy is unsuitable rather than the NICE scoped population. The trial was international and undertaken in 21 countries, there were 6 United Kingdom (UK) sites and 8 UK participants; there may be reduced generalisability to the NHS population because of this. Some patients in the trial may have been eligible for FCR/BR therapy in the UK and therefore may be slightly healthier than the UK population unsuitable for FCR/BR. Also, in practice the decision about whether a patient is suitable for FCR/BR therapy is based on an end-of-bed assessment, and is not necessarily well-reflected in the CIRS cut off used in CLL14.

The CS undertook a feasibility assessment to determine the suitability of available data for an indirect comparison to ibrutinib in the del(17p)/TP53 mutation subgroup. The ERG agrees that an anchored comparison is not possible and that an unanchored match adjusted indirect comparison is also not ideal.

Three studies with subgroups of relevance were identified and compared with CLL14 via a naïve comparison. The ERG considers it uncertain whether the subgroups in these studies are comparable with the CLL14 del(17p)/TP53 mutation subgroup. In addition, the ERG notes that there are a number of inaccuracies in the description of the Ahn 2018 study by the CS. There is heterogeneity between these studies and CLL14 in terms of study design, eligibility criteria, outcomes and possible heterogeneity in baseline characteristics.

The company performed the indirect comparison using hazard ratios but the data are currently insufficient to conclude whether hazard ratios accurately capture the differences between the treatments. Also, there was no patient level data for the comparator participants and the data were obtained from digitising graphs which is another source of uncertainty.

Overall, caution is recommended in the interpretation of these indirect comparisons.

1.4 Summary of cost effectiveness submitted evidence by the company

Evidence on cost-effectiveness was received on the following occasions:

- The original CS, which was based on CLL14 evidence from the August 2018 data cut.
- Responses to ERG's request for clarifications on the original CS.
- The CS addendum, presenting an updated analysis taking into account a new data cut-off (August 2019)
- Responses to ERG's request for clarifications on the CS addendum.

Economic models were made available with the original submission (based on the August 2018 data-cut), with the CS addendum and with the company's response to clarification queries on the original CS and CS addendum.

The submitted evidence pertains to two distinct subgroups: 1) patients without a del(17p)/TP53 mutation and 2) those patients with a del(17p)/TP53 mutation. Treatments compared for the first subgroup are VenG and GClb. Treatments compared for the second subgroup are VenG and ibrutinib.

The company carried out a systematic literature review of cost-effectiveness evidence, aiming to identify studies on previously untreated CLL that reported relevant economic evaluations,

health-related quality of life (HRQoL) or costs and use of health care resources. The review identified 43 relevant economic evaluations, 20 studies providing information on HRQoL and 16 studies giving estimates of healthcare resource use and costs. The company concluded that none of the identified economic evaluations pertained to the exact decision problem of interest in this submission. Information identified through the review, including evidence from completed NICE technology appraisals in CLL, was used in the economic analysis.

The economic model submitted follows a partitioned survival approach and comprises three health states: (i) progression-free survival, (ii) post-progression survival and (iii) death. The distribution of the patient population within each of the three health states at each point in time is guided by extrapolated progression-free survival (PFS) and overall survival (OS) curves. Time-to-next treatment curves were also used to calculate the point in time when subsequent treatment was initiated. Death due to causes other than CLL (i.e. background mortality) was guided by age-adjusted and sex-adjusted mortality risk values drawn from UK life tables. The model adopted a NHS and personal social services perspective, uses a 28-day cycle length, has a time horizon of 30 years and discounted future costs and benefits at 3.5% per annum (in the base-case analysis).

The same model structure was used to evaluate the cost-effectiveness of the compared treatments (VenG vs GClb in patients without del(17p)/TP53 mutation; VenG vs ibrutinib in patients with del(17p)/TP53 mutation). The algorithm used to categorise patients to groups according to mutation status differed between the clinical study report analysis and the cost-effectiveness modelling analysis.

Time to event parameter estimates used in the model were obtained from the CLL14 trial (August 2018 data cut in the original CS, August 2019 data cut in subsequent addendum). For the non-del(17p)/TP53 mutation population (VenG vs GClb), PFS and OS were informed by data from the CLL14 trial and were parameterised using an independent model (log-logistic) and a dependent model (exponential), respectively. For OS, the company used the predicted curve for the GClb arm to represent OS for both arms. Time-to-next treatment (TTNT) was extrapolated using an independent (log-logistic) model applied to CLL14 data for both VenG and GClb arms. All curves were constrained such that their hazard rates could not fall below background mortality. For the del(17p)/TP53 mutation population (VenG vs ibrutinib), the company pointed out that the limited evidence of ibrutinib in the untreated CLL with del(17p)/TP53 mutation population made network meta-analyses and matched adjusted indirect comparison

unfeasible. A naïve comparison of VenG versus ibrutinib was performed using a published study by Mato et al.

Preference-based quality of life (utility) values for different health states were collected in the CLL14 trial using the EuroQol EQ-5D-3L instrument. However, the company considered that the utility estimates were notably higher than those accepted in previous appraisals and published UK age-adjusted general population values. Instead, a decision was made to use health state utilities values for the pre-progression (PFS) and post-progression (PPS) states from the available literature. Utility values relating to pre-progression status were further broken down by treatment receiving status (on treatment, off treatment) and type of treatment (intravenous or oral).

The following key categories of resource use and costs were included in the company's analysis: (i) intervention and comparators' costs (including treatment acquisition and administration costs, routine care costs, tumour lysis syndrome (TLS) monitoring costs and subsequent treatment costs), (ii) costs related to adverse events, and (iii) terminal care costs. Unit costs of drugs comprising VenG and its comparators were sourced from the British National Formulary (BNF). Administration costs were included in the model for the treatments delivered intravenously. Routine care and monitoring costs included services such as scans, blood tests, transfusions and consultations. The cost of TLS prophylaxis was calculated based on an algorithm that categorised patients by risk of developing TLS according to data observed in the treated CLL14. Subsequent treatment costs were calculated according to the type of subsequent treatment mix received, the point in time when subsequent treatment would be initiated and the length of time over which subsequent treatment would be administered. In the non-del(17p)/TP53 mutation population, input for these calculations was derived from time-to-event data observed in CLL14 (TTNT and OS). In the del(17p)/TP53 mutation population, the proportion of ibrutinib patients who receive subsequent treatment was calculated as the difference in the ibrutinib PPS duration and OS curves.

On the basis of list prices for all treatments, the company reported the following results. In the non-del(17p)/TP53 mutation population, VenG is associated with a greater number of QALYs and lower costs than GClb, thus, VenG is dominant versus GClb. In this population, VenG resulted in a positive net monetary benefit (NMB) of [redacted] at a willingness-to-pay threshold of £30,000 per QALY. In the del(17p)/TP53 mutation population, VenG is associated with a lower number of QALYs and lower costs versus ibrutinib. In this population, VenG was associated with

a positive NMB of [redacted] at a willingness-to-pay threshold of £30,000 per QALY. Sensitivity and scenario analyses reported by the company showed that, on the whole, results are robust to alternative values and assumptions.

1.4.1 Summary of the ERG's critique of cost-effectiveness evidence submitted

The following key points in relation to cost-effectiveness evidence presented by the company have been discussed in the ERG's critique and are summarised here:

- Systematic literature reviews carried out by the company to identify existing evidence on economic evaluations, costs and HRQoL were comprehensive. The ERG accepts that no directly relevant economic evaluations are available and agrees that developing a *de novo* economic model tailored to the requirements of the specific final scope and decision problem was necessary.
- The ERG believe that the type and structure of the submitted model (three state partitioned survival model) is appropriate for the purposes of the condition investigated and adequate for the decision problem considered in this appraisal. The pathway employed in the model is, in general, in line with expectations around the clinical progression of the disease, while the structure of the model is generally suitable for capturing and quantifying key costs and health outcomes associated with the compared treatments.
- More broadly, the analytic methods used in the economic analysis (evaluated time horizon, discounting, evaluation of costs and outcomes) are generally in line with the NICE Guide to Methods of Technology Appraisal and previous NICE TAs.
- Different approaches for categorising CLL14 patients according to mutation status were used in the clinical study report analysis and the economic model, resulting in differences in the numbers of patients included in the defined populations with and without del(17p)/TP53 mutation. However, the data resulting from the different categorisations had a small, inconsequential impact on the final cost-effectiveness results.
- Immaturity of data (in VenG vs. GClb), reliance on an unadjusted naïve indirect comparison (for VenG vs ibrutinib) and the uncertainty arising as a result have an inevitable effect on cost-effectiveness calculations. Time-to-event data are drivers of incremental costs and outcomes in the decision model. Limitations in currently available data make it difficult to draw a complete and reliable picture of each treatment's

effectiveness and they inevitably affect the final cost-effectiveness results. The ERG has identified extrapolations that, we believe, are more plausible and appropriate; these have been incorporated in the ERG's preferred base-case analysis.

- Health state utility values were sourced from the literature, rather than from the EQ-5D data collected in the CLL14 trial. The justification for not using CLL14 trial observations is considered to be reasonable. QALY decrements due to adverse events were appropriately applied. In response to clarification questions, the company offered a more pragmatic reflection of utility values in the pre-progression health state, which takes into account whether patients are off or on treatment and the type of treatment received (intravenous or oral). However, the ERG consider the utility value assigned to reflect the 'progression-free, off treatment' status to be problematic. An alternative value has been put forward as a more plausible estimate in the ERG's base-case analysis.
- A number of resource use components and their relevant costs were identified and taken into account in the cost calculations. These included acquisition and administration costs for first and second line treatments, routine care and tests, cost of TLS prophylaxis and terminal care costs. Elements of the calculations and methods used are in line with previous NICE Technology Appraisals in CLL. An inconsistency in the calculation of subsequent treatment costs for patients on ibrutinib first line treatment has been pointed out.
- The company took a number of steps to validate the submitted economic model. Additional checks were carried out by the ERG. The ERG agree that steps undertaken by the company to ensure the validity of the model are appropriate. Putting aside limitations in the analysis due to data immaturity and unavailability, the ERG deem the model's validity to be, on the whole, sound.
- The company carried out probabilistic, deterministic and scenario analyses. Issues identified around the specified level of uncertainty across a range of diverse parameters were raised in the ERG's clarification questions and corrections were made by the company. In general, sensitivity analyses suggested that the results are robust to a wide range of alternative values and approaches.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

Evidence presented by the company presented the following strengths:

- The review methods employed in the company systematic literature review were appropriate and there is a low risk of systematic error in the results of the review.
- The included trial (CLL14) was well designed and has a low risk of bias within the limits of an open label design. It is suitably powered to answer the primary hypothesis.
- The model type and structure were appropriate for the decision problem.
- Where available, key evidence on treatment effectiveness was drawn from the CLL14 trial.
- Resource use and costs calculations were in agreement with NICE technology appraisals in CLL.
- Extensive sensitivity and scenario were carried out to assess the robustness of the results to different assumptions, methods and parameter values.

1.5.2 Weaknesses and areas of uncertainty

Evidence submitted by the company presented the following key weaknesses:

- The CS used the whole trial population from the CLL14 trial, which included those with and those without del(17p)/TP53 mutation, for the subpopulation of people without the del(17p)/TP53 mutation comparing VenG with GClb. It is unclear what effect this may have on the results, although the ERG notes that the numbers with del(17p)/TP53 mutation were small. There is also double counting of participants with del(17p)/TP53 mutation as these are then used separately in the analysis comparing with ibrutinib.
- The CLL14 trial is ongoing and data are immature for some of the key outcomes of relevance to the decision problem. The assessment of proportional hazards is not clearly reported for some outcomes. The reasons for, and level of, dose reductions or alterations of the treatments within the CLL14 trial are not reported for all treatments consistently and the impact of these modifications is uncertain.
- There is no head-to-head comparison between VenG and ibrutinib and a naïve indirect comparison was undertaken. The results of this indirect comparison are very uncertain owing to the methodological approaches used and likely heterogeneity between populations; this is reflected in the wide confidence intervals seen and results should therefore be interpreted with caution.
- Immaturity of data (in VenG vs. GClb), use of a naïve indirect comparison (for VenG vs ibrutinib) and the uncertainty arising as a result, mean that key time-to-event data which are drivers of incremental costs and outcomes in the decision model may not be

appropriate. To the extent possible, the ERG has identified extrapolations that are deemed to be more appropriate.

- Due to unexpectedly high preference-based health related quality of life (EQ-5D-3L) values observed in the CLL14 trial, health state utilities were sourced from the literature. The ERG disagreed with the value chosen to reflect utility in patients who had not progressed and were off treatment, which is deemed to be inappropriately high.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

To address issues identified in the economic analysis submitted by the company, the ERG implemented changes that formed the ERG's preferred base-case analysis. Amendments were made to the utility value for the 'pre-progression, off treatment' status and in time-to-event parameters and extrapolations in both the non-del(17p)/TP53 and del(17p)/TP53 mutation populations.

In the non-del(17p)/TP53 mutation population, implementing the ERG's preferred base-case resulted in reductions in incremental costs and QALYs compared to the company's base-case values, leading to an overall reduction in NMB (at list prices for all treatments and a willingness-to-pay value £30,000 per QALY) by [redacted] compared to the company's base-case results ([redacted] vs [redacted]). In both the company's base-case analysis and the ERG's base-case analysis, VenG was dominant against GClb.

In the del(17p)/TP53 mutation population, implementing the ERG's preferred base-case resulted in reductions in both incremental costs (cost savings) and QALYs (VenG vs ibrutinib) compared to the company's base-case values, leading to an overall reduction in NMB (at list prices for all treatments and a willingness-to-pay value £30,000 per QALY) by approximately [redacted] compared to the company's base-case results ([redacted] vs [redacted]). The ICER for this comparison falls within the south-west quadrant of the cost-effectiveness plane reflecting cost savings per QALY forgone.

Additional scenario analyses carried out by the ERG led to results that agreed in direction with the results of the company's and the ERG's base-case analyses. No additional, non-quantifiable variables that may have a consequential change in the results were identified.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The CS provides an overview and description of the epidemiology of chronic lymphocytic leukaemia (CLL) (CS B.1.3.1), noting that it is a clonal disease [i.e. involving development of identical cells] of unknown aetiology characterised by the accumulation of mature B cells in blood, lymph nodes, spleen liver and bone marrow. This leads to leucocytosis [increase in white blood cells], lymphadenopathy [abnormal lymph nodes], hepatosplenomegaly [swelling of liver and spleen], anaemia [decrease in red blood cells or haemoglobin], thrombocytopenia [platelets deficiency], neutropenia [reduced neutrophils leading to increased susceptibility to infection], bone marrow failure [insufficient red blood cells, white blood cells or platelets produced] and symptoms as described below.

The CS describes some of the genetic abnormalities that can be identified in CLL, namely mutation of the TP53 gene via deletion of the short arm of chromosome 17 [del(17p)] (which contains the TP53 gene) or mutation of the TP53 gene sequence. About 5-10% of CLL patients have TP53 dysregulation at diagnosis[1] and it is associated with poor prognosis; chemoimmunotherapy is ineffective in these patients.[2]

The CS does not describe immunoglobulin heavy chain gene variable region (IGHV) mutation. This is a known prognostic marker, with IGHV-mutated CLL associated with better prognosis and slower growing disease. Retrospective studies suggest that patients with mutated IGHV can experience prolonged remissions with chemotherapy.[2] The ERG clinical advisor states that it is now increasingly tested for in routine clinical care within the NHS.

The CS notes that CLL is the most common of the chronic leukaemias. It reports the European age-standardised incidence in the UK as 6.0 per 100,000 in 2016, with 3,412 new cases in England and Wales alone.[3] It is more common in men than women, with a ratio of 1.7: 1. The risk increases with age; with 42% of new cases in people aged 75 and over and the highest incidence in women aged 85 to 89 and men aged over 90.[3]

The CS states that most CLL patients are older than 70 and have relevant coexisting conditions, but does not describe details of frequency and type of coexisting conditions in CLL. Co-morbidities can affect an individual's fitness for chemotherapy, and treatment options differ for those fit for chemotherapy (or 'suitable for') and those unfit (unsuitable) for chemotherapy (see

below). However, as the CS acknowledges, there is no optimal strategy or agreed co-morbidity assessment tool to determine fitness for chemotherapy.[2] According to the ERG clinical expert, in UK practice clinicians rely on 'end of the bed assessment' which is difficult to quantify. In addition to specific co-morbidities, other factors such as poor performance status / exercise capacity, poor bone marrow reserve, contraindications to treatment and desire to avoid intravenous chemotherapy or regular hospital attendance for treatment may also make a patient unsuitable for certain treatments.

The CS describes the disease burden (CS B.1.3.2). Most patients are asymptomatic at diagnosis and are diagnosed by chance through routine blood tests. Symptoms that can appear as the disease progresses include swollen lymph nodes, recurrent infections and systemic symptoms (fatigue, loss of appetite, weight loss, night sweats and shortness of breath when exercising).

The CS describes the impact of CLL on the patient's quality of life and ability to work. The CS reports findings from a large prospective survey of people with CLL which showed that disease progression has a negative impact on health-related quality of life (HRQoL).[4] The study also showed that people with CLL have lower emotional wellbeing than the general population and people with other cancer types, although this comparison was made with historical controls.[4] However, the CS does not report that the survey also found similar physical, social/family, functional, and overall quality of life (QOL) scores for CLL patients and those from published population norms.[4]

The CS cites evidence that an additional burden for people with CLL is the impact on the ability to work.[5] This evidence source is a guide for patients produced by the Leukaemia Care charity and discusses how people with CLL may require temporary sick leave, reduction in working hours or need reasonable adjustments to be made at work. The CS hypothesises that these factors may have an impact on finances and emotional burden of people with CLL, which seems reasonable, but the CS does not present any evidence to support this.

Overall, the ERG considers that the company's description of the underlying health problem is appropriate and relevant to the decision problem under consideration.

2.1 Critique of company's overview of current service provision

The CS describes the current UK CLL clinical pathway of care (CS B.1.3.4 and summarised in CS Figure 1), including diagnosis and staging, initiation of treatment and determining fitness status for chemotherapy. Treatments recommended by NICE and by British Society of Haematology (BSH) guidelines[2] are outlined in CS Table 2 together with their relevance to the current submission. Treatment of previously untreated CLL patients is described for the following groups:

- *Fit patients without del(17p)/TP53 mutation:*

The CS refers to BSH guidelines[2] for treatment with fludarabine, cyclophosphamide and rituximab (FCR) and bendamustine and rituximab (BR), which are listed as treatment options for this group in the NICE scope. However, the NICE scope also lists treatment with chlorambucil with or without rituximab, which is not mentioned by the CS. The company considers that this population is not relevant to the submission, as the population of the pivotal CLL14 trial had characteristics that would typically make then unsuitable for FCR and BR. However, the ERG clinical expert considers that this patient group would be relevant to this appraisal (see section 3.1).

- *FCR/BR unsuitable patients without del(17p)/TP53 mutation:*

In line with BSH guidelines[2] and the NICE scope, the CS notes that obinutuzumab with chlorambucil (GClb) is the standard of care in this group.

- *Patients with del(17p)/TP53 mutation:*

The CS notes that NICE recommends ibrutinib monotherapy for people for whom chemoimmunotherapy is unsuitable, and idelalisib with rituximab for people who cannot have other therapies. The CS argues that the latter has now been superseded by ibrutinib due to a higher risk of infection and death than other therapies. The ERG clinical expert agrees with this statement. The CS notes that the BSH guidelines[2] also recommend ibrutinib in this population.

The ERG considers that the company's overview of current service provision is appropriate and relevant to the decision problem under consideration.

Unmet need

The company describes the unmet need for treatment options for previously untreated CLL (B.1.3.5), particularly for those with del(17p)/TP53 mutation and those without del(17p)/TP53 mutation but with comorbid conditions rendering them unsuitable for FCR/BR. In addition,

there is an unmet need for patients with del(17p)/TP53 mutation who cannot tolerate ibrutinib (such as those with cardiac risk factors). The company also states there is a high unmet need for treatments that improve progression free survival (PFS) and have potential to achieve undetectable minimal residual disease (see section 4.2.1) in both those with and without del(17p)/TP53 mutation. The ERG clinical advisor agrees with this statement, noting that whilst long-term remission can be achieved with FCR, there is a desire to move to non-chemoimmunotherapy treatments and therefore a need for treatment options for all patients with untreated CLL, regardless of suitability for FCR/BR treatment or mutation status. The company describes how the CLL14 pivotal trial demonstrates that venetoclax plus obinutuzumab (VenG) has the potential to meet the high unmet need in untreated CLL; the ERG reviews this evidence in section 4.2.

Treatment pathway of venetoclax and obinutuzumab (VenG)

The rationale for the treatment combination of VenG is described in the CLL14 trial protocol. Venetoclax is a selective inhibitor of B-cell lymphoma-2, a protein which is overexpressed in approximately 95% of CLL cases.[6] Obinutuzumab is a monoclonal antibody which is directed at the CD20 antigen which is found on most malignant cells of B-cell origin.[7] These different mechanisms were anticipated to improve tumour response in CLL and therefore delay progression and avoid resistance. The treatment combination also allows a chemotherapy-free regimen.

The company presents the current treatment pathway for CLL in the NHS and the positioning of VenG in CS Figure 1. The company states that the anticipated positioning of VenG is:

- For the treatment of previously untreated FCR/BR-unsuitable patients without del(17p)/TP53 mutation
- For the treatment of previously untreated patients with del(17p)/TP53 mutation

The company notes that the anticipated marketing authorisation includes people who would be eligible for FCR/BR (see section 3.1), but considers it likely that in NHS practice VenG will be used in line with the CLL14 study, in which the majority were considered unsuitable for FCR/BR. However, the ERG clinical advisor considers it likely that in practice VenG will be used in younger fitter/patients than those in the CLL14 trial.

3 Critique of company's definition of decision problem

The company's decision problem is largely consistent with the NICE scope, although there are some key differences.

3.1 Population

The population in the company's decision problem is people with untreated CLL with coexisting conditions that make fludarabine and bendamustine based therapy unsuitable.

This is narrower than the NICE scope (people with untreated CLL) but is in line with the population of the pivotal CLL14 trial and with the company's anticipated positioning of VenG in the NHS treatment pathway. However, the anticipated marketing authorisation wording does not specify unsuitability for fludarabine/bendamustine based therapy (see below). The ERG's clinical advisor considered that in UK practice some clinicians are keen to use VenG as a treatment option for patients who are younger/fitter than those in the CLL14 trial, however there is no evidence for use in this population. The NICE scope does not limit by age, but the CS and the anticipated marketing authorisation are limited to adults.

3.2 Intervention

Venetoclax (Venclyxto) with obinutuzumab (VenG). The marketing authorisation is: Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. Committee for Medicinal Products for Human Use (CHMP) positive opinion was granted in January 2020, and marketing authorisation in this indication was granted in March 2020.

3.3 Comparators

The company's decision problem includes the comparators according to the following subgroups:

- Without a del(17p)/TP53 mutation: obinutuzumab with chlorambucil
- With a del(17p)/TP53 mutation: ibrutinib

The NICE scope also lists the following comparators. These were excluded by the company with justification as follows:

Without a del(17p)/TP53 mutation

- Fludarabine, cyclophosphamide and rituximab (FCR): the CLL14 trial excludes patients who would normally be suitable for FCR. The evidence submission is for FCR/BR-unsuitable patients only.
- Bendamustine with or without rituximab (BR), for people for whom fludarabine-based therapy is unsuitable: the evidence submission is for FCR/BR-unsuitable patients only.
- Chlorambucil with or without rituximab, for people for whom fludarabine-based therapy is unsuitable: not recommended according to BSH guidelines 2018[2]

With a del(17p)/TP53 mutation

- Idelalisib with rituximab: this has been superseded by treatment with ibrutinib (BSH guidelines 2018[2])

The ERG clinical advisor agrees that it is appropriate to exclude these comparators, but notes that there is a high variability in treatment in current practice. It is also likely that some patients in CLL14 may have been considered suitable for FCR/BR therapy had they been treated routinely in the UK, but it is impossible to quantify this number of patients from summary data.

3.4 Outcomes

Overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life, as per the NICE scope.

3.5 Other relevant factors

The NICE scope and the company's decision problem specify the following subgroups:

- People with untreated CLL with del(17p)/TP53 mutation
- People with untreated CLL for whom fludarabine-based therapy is unsuitable
- People with untreated CLL for whom bendamustine-based therapy is unsuitable.

The first subgroup, people with untreated CLL with del(17p)/TP53 mutation, was a pre-specified subgroup in the CLL14 trial and is considered in the CS. However, the algorithm for identifying the del(17p)/TP53 mutation subgroup differs between the clinical and cost-effectiveness sections, resulting in differing sample sizes (see section 5.2.3 for details). The

rationale for using different algorithms is not adequately justified by the company, although it has little impact on the results.

The other two subgroups, people with untreated CLL for whom fludarabine-based therapy is unsuitable and CLL for whom bendamustine-based therapy is unsuitable, are not addressed separately in the submission, although the CLL14 trial population is considered to be unsuitable for FCR/BR (fludarabine-based/bendamustine-based therapies respectively).

The CS does not include a section on equality considerations. The ERG is not aware of any potential equality considerations for the use of VenG in the UK.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

A summary of the ERG's quality assessment of the company's systematic review of clinical evidence is presented in Table 1. The methods of the review were considered appropriate, including searches undertaken and the use of two reviewers for study selection and data extraction, therefore the risk of systematic error in the results of the review is low. The submitted evidence generally reflects the decision problem, although there are differences from the NICE scope in terms of the population and eligible comparators. This is discussed below.

Table 1 Quality assessment of the company's systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes (although additional references were identified by ERG update searches)
3. Is the validity of included studies adequately assessed?	Yes
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.1 Searches

A broad systematic literature review (SLR) was conducted to capture all available evidence for the efficacy, safety and tolerability of all treatments, including those outside of the scope of the company submission, for previously untreated CLL in adults across all populations. The search was not restricted to the two subpopulations considered in the company submission (B1, Table 1).

Searches were conducted in December 2018 with update searches in July 2019. A range of relevant databases were searched: Medline (including Medline In Process), EMBASE, DARE,

NHS-EED, HTA and The Cochrane Library. The ERG note that no trial databases were searched but deem these sources to be appropriate for the identification of relevant literature. Abstracts of major conferences between 2016 and July 2019 were hand searched, as well as the bibliographic references of the systematic and non-systematic reviews found at title-abstract stage. At the full text stage, Letters to editors were searched for RCTs and single-arm studies.

A combination of relevant index and free text terms were used for the main database searches. The search terms for CLL were not as sensitive as the search terms used in a recent Cochrane review [8]. The search was limited by randomised and non-randomised trials. Conference abstracts were excluded from the results, although selected conferences were hand searched. A more limited search was conducted in the Cochrane Library via CENTRAL and Cochrane Database of Systematic Reviews (CDSR).

A total of 150 references were included in the SLR comprised of 56 RCTs (from 36 unique studies) and 94 non-RCT studies (comprising of 80 unique studies). Only 7 references were relevant to the decision problem. 4 references reported one unique study (CLL14) and 3 references reported 3 unique studies (D1.2, Table 8).

CS Appendix Table 7 (CS Appendix D1.2) lists the 150 studies included in the initial clinical SLR but are not of relevance to the decision problem or the submission, but incorrectly includes the eight publications included in the indirect comparison (listed in CS Table 8) (clarification response A28).

4.1.2 Inclusion criteria

The company conducted a broad systematic literature review that aimed to identify studies of all treatments for previously untreated CLL using criteria listed in CS Appendix Table 5 and summarised here:

Population

Established first-line CLL (CLL or b-cell CLL or small lymphocytic lymphoma (SLL)). Inclusion was limited to adults aged ≥18 years (paediatric studies and those where the average age of the population was <18 years were excluded, although the inclusion of individual patients <18 years in an otherwise adult population was allowed). This is in line with the population of CLL14, however it is narrower than the NICE scope which does not limit by age.

Interventions and comparators

A list of twenty interventions were eligible, including all those specified in the NICE scope. Any treatment, no treatment and placebo were eligible comparators.

Outcomes

A list of 21 outcomes were eligible, including most of those specified by the NICE scope (OS, PFS, response rate, and adverse effects). However, HRQoL was not stated. This may mean that relevant studies reporting only HRQoL measures were missed by the company searches, however, a separate SLR of HRQoL was undertaken to inform the economic model.

Study design

Clinical trials and observational studies were eligible.

Other

Only full-text articles and publications in English language were eligible. While this may increase the risk of publication bias, the ERG considers it to be a pragmatic approach.

A two-stage approach was applied to eligibility screening, a flow diagram of study selection is presented in CS Appendix Figure 1. A total of 170 records were initially excluded at full-text review based on the above criteria (a list of these excluded studies and reasons for exclusion was provided in CS Appendix Table 6). The remaining set of 150 records was then limited to studies of:

- VenG and GClb for patients without del(17p)/TP53 mutation
- VenG and ibrutinib for patients with del(17p)/TP53 mutation

A total of 143 records were excluded at this stage, and 7 records were included (reporting 4 unique studies: 1 RCT and 3 non-RCTs).

CS Appendix Table 7 lists all 150 studies identified and included at the initial stage, not just those subsequently excluded because they do not present comparisons of relevance as stated in CS Appendix D.1.2. Reasons for exclusion of the 143 studies subsequently excluded were not given and pdfs of the excluded studies were not provided by the company. The ERG requested

pdfs of any excluded ibrutinib studies regardless of line of therapy (provided in clarification response A14) and checked eligibility. A single-arm study of VenG[9] excluded by the company is summarised by the ERG in section 4.8.

The following comparators specified by the NICE scope were excluded from the company's literature review (see Decision Problem section 3.3 for discussion of this):

- fludarabine, cyclophosphamide and rituximab (FCR)
- bendamustine with or without rituximab (BR), for people for whom fludarabine-based therapy is unsuitable
- chlorambucil with or without rituximab, for people for whom fludarabine-based therapy is unsuitable
- idelalisib with rituximab.

The company has not been explicit about any potential bias in the selection of the studies; however, study selection was undertaken by two independent reviewers.

4.1.3 Critique of data extraction

Data extraction of pre-specified data into extraction tables was undertaken by one reviewer and checked by a second reviewer. The ERG considers the approach to be appropriate.

4.1.4 Quality assessment

The CS provides a risk of bias assessment of CLL14 using the NICE suggested criteria, which include aspects assessing randomisation bias, performance bias and detection bias amongst others. A comparison of the CS and the ERG assessments of the trial is in Table 2.

Overall, the CS considers the CLL14 trial as having a low risk of bias. The ERG generally agrees with this assessment, however notes the performance bias and detection bias inherent in an open label trial. The ERG disagrees with one of the company's judgements as seen in Table 2; the ERG considers that there is a risk of bias due to selective outcome reporting. The ERG also notes that although the arms are balanced with respect to key prognostic factors, there are some differences between groups in baseline comorbidities.

Table 2 CS and ERG risk of bias assessment of CLL14 trial

	CS Response	ERG response
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes (in terms of key prognostic factors such as age, sex, mutation status). However, comorbidities were unbalanced (vascular disorders, hypercholesterolaemia, respiratory disorders, psychiatric disorders all >5% difference between groups)
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No (although Independent Review Committee (IRC) assessments were blinded to allocation)
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Yes (published protocol and NCT record lists overall response rate (ORR) at completion of combination treatment assessment, MRD at completion of combination treatment assessment but no reference to these data)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified one randomised controlled trial (RCT) (CLL14 trial[10]) which was funded by F. Hoffmann–La Roche and AbbVie Inc. The CLL14 trial compares VenG with GClb in people with known comorbidities that makes them unsuitable for treatment with FCR/BR. In response to clarification question A1, the company confirmed there is no single strategy to confirm suitability for chemotherapy but that participants in the trial had at least one significant co-morbidity that could impact suitability. The trial includes mostly people without del(17p)/TP53 mutation and also a smaller proportion with del(17p)/TP53 mutation. As discussed, the whole trial population is used as evidence for the subpopulation of people without del(17p)/TP53 mutation compared with GClb. The subgroup with del(17p)/TP53 mutation is also used via a naïve indirect comparison with ibrutinib monotherapy – see section 4.4. The evidence for

subpopulation without del(17p)/TP53 mutation therefore includes a proportion of participants with del(17p)/TP53 mutation.

The CS summarises the CLL14 trial in B.2.2 to B.2.7 and further details are reported in CS Appendix D2, D3 and L. In addition, electronic copies of the RCT publication (primary reference Fischer et al 2019[7]) and the confidential Clinical Study Report (CSR)[10] were provided to the ERG, plus a CS addendum and CSR supplement with longer follow-up.

The CLL14 trial is an open label RCT undertaken in people with previously untreated CLL and coexisting medical conditions. The concurrent medical conditions of participants were summarised in B.2.3.6 and Table 10 of the CS and include hypertension, hypercholesterolaemia, cardiac disorders and chronic obstructive pulmonary disease (COPD), see baseline characteristics Table 3 for further details. The ERG clinical expert confirms that these co-existing medical conditions would render the participants unsuitable for treatment with FCR/BR. A concurrent medical condition at baseline was reported in all patients apart from one in the GClb arm (clarification A1).

All participants were aged 18 years or older. They had a life expectancy of more than 6 months, with CLL that required treatment (International Workshop CLL criteria[11]), the presence of coexisting conditions and a total cumulative illness rating scale (CIRS) of >6 (the total score ranges from 0 to 56) or creatinine clearance <70 mL/min. Clinical advice to the ERG is that the latter criterion (CIRS score cut-off of >6 or creatinine clearance <70 ml/min) is not typically used in UK clinical practice to determine lack of suitability for FCR/BR treatment because there is no standard assessment – patients with CLL are assessed individually to include all relevant factors. Our clinical expert considered it likely that some of these patients may have been eligible for FCR/BR treatment in the UK, therefore the trial population may be slightly healthier than the UK population unsuitable for FCR/BR.

The trial had an initial run-in phase where 12 participants received VenG for three cycles to assess safety. Randomisation then proceeded but the CS is unclear whether these 12 participants were included in the RCT. The company confirmed they were not included in the main randomisation phase (clarification response A2). Results from these participants were published[12] although this was not stated in the CS (see section 4.2.1). The trial randomised 216 participants to VenG and 216 participants to GClb. Four participants in the VenG arm and two in the GClb arm did not receive the randomised treatment (reasons provided, CS Appendix Figure

4) but were included in the efficacy analysis (Intention to treat, ITT). At the August 2019 data cut (when all participants had completed 12 cycles of treatment and had a median of 39.6 months follow-up) 177 participants remained in follow-up in the VenG arm and 178 in the GClb arm. There were similar rates and reasons for losses to follow-up across arms.

All participants received intravenous obinutuzumab which was administered for 6 cycles. For cycle 1, 1000 mg was given on days 1 (or 100 mg on day 1 and 900 mg on day 2), day 8 and day 15. Thereafter 1000 mg was given on day 1 of each cycle. Overnight hospitalisation may be required following the first infusion of cycle 1.

For the VenG arm, oral venetoclax was started on day 22 of cycle 1 with an initial ramp-up period (1 week each of 20, 50, 100 and 200 mg daily) then 400 mg daily until the end of cycle 12. The draft summary of product characteristics (SPC) for VenG notes that there is a risk of tumour lysis syndrome (TLS) with venetoclax treatment and describes prophylaxis measures and dose modifications for TLS. People with a high tumour burden and/or reduced renal function have a greater risk of TLS, which occurs when a large number of cancer cells die within a short period, releasing their contents in to the blood. In CLL14, participants deemed at high risk of TLS had the 20 mg and 50 mg doses in hospital (high risk was defined by radiological assessment as any measurable lymph node with the largest diameter ≥ 10 cm or the presence of both ≥ 25 × 109/L absolute lymphocyte count AND any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm). The dosing of venetoclax was based on the findings from a dose-finding phase I study of venetoclax monotherapy in relapsed or refractory CLL or non-Hodgkin lymphoma.[13]

For the GClb arm, oral chlorambucil (Clb) was administered on days 1 and 15 of each cycle until the end of the 12th cycle at a dose of 0.5 mg/kg. However, this schedule, is not aligned with Clb use in UK clinical practice, where the drug is typically administered over six cycles.

All cycles were 28 days and no cross-overs were permitted.

The CS (B.2.10.2) describes the proportions of participants with dose modification (dose interruption or reduction) of venetoclax, chlorambucil and obinutuzumab during the trial (see Adverse Events section 4.7 for treatment exposure) but there are no details of what the level of dose reductions or alterations were or whether these modifications were defined in the trial protocol. The trial protocol describes permitted dose reductions for adverse events and for TLS,

and the CS reports that at least half of these modifications for one or more of the treatments were for adverse events. The reasons for the remaining dose modifications are not reported. The CS also describes the proportion of participants not reaching the target doses for the three drugs respectively.

The number of patients who discontinued at least one treatment component per treatment arm was 47 (21.8%) for VenG versus 54 (25%) for GClb. The main reasons for discontinuation were adverse events (VenG n=31 versus GClb n=34) or withdrawal of consent (VenG n=9 versus GClb n=11), see CS Appendix Figure 4.

The trial was international and undertaken in 196 sites in 21 countries, including North and South American countries, European countries, and Australia and New Zealand. There were 6 UK sites and 8 UK participants.

Follow-up of the CLL14 trial is currently ongoing; analysis at August 2018 and August 2019 data-cuts have been presented.

Baseline characteristics were similar between groups (Table 3) with the exception of some comorbidities. The CS highlights that there was an imbalance between groups for vascular (specifically hypertension), respiratory, thoracic and mediastinal disorders (in particular COPD and asthma) and for psychiatric disorders (specifically insomnia). All of these were more common in the VenG group. The ERG clinical advisor notes that this may impact on the rate of infective adverse events with greater risk in the VenG group. Additional details of comorbidities were provided in response to clarification A1; these appear balanced between groups.

The numbers of patients with TP53 mutation and del(17p)/TP53 mutation in the CS and CSR are incorrect (101 patients with TP53 mutation were incorrectly categorised as 'unknown'); the company provides an explanation and corrected baseline characteristics and results in clarification response A4. The corrected proportions of patients in each arm with del(17p), TP53 mutation, and del(17p)/TP53 mutation are summarised in Table 3. For completeness, the ERG requested the number of patients in each arm who have both del(17p) and TP53 mutation, but the company did not provide this.

Table 3 summarises corrected key baseline characteristics for the subgroup with del(17p)/TP53 mutation (n=49). There are some imbalances between arms for this subgroup ([redacted]), however for this subgroup it is the comparison with ibrutinib that is relevant to this appraisal (see section 4.5), rather than the comparison with GClb. In clarification response A4 the company provides baseline characteristics and results (PFS and OS) for the subgroup without del(17p)/TP53 mutation (n=368) and the subgroup with these data missing data (n=15); these data have not been summarised in the ERG report.

Table 3 Key baseline characteristics of the CLL14 trial and the del(17p)/TP53 mutation subgroup

% unless stated	Full study population		Subgroup with del(17p)/TP53 mutation	
	VenG (N=216)	GClb (N= 216)	VenG (N= [redacted])	GClb (N= [redacted])
Median (range) Age ≥65 years Age ≥75 years	[redacted] 33.3	[redacted] 36.1	[redacted]	[redacted]
Male sex	67.6	66.2	[redacted]	[redacted]
Median time from diagnosis, months (range)	31.2 (0.4–214.7)	29.2 (0.3–244.8)	[redacted]	[redacted]
High TLS risk	22.2	19.9	[redacted]	[redacted]
Total CIRS score >6	86.1	81.9	[redacted]	[redacted]
Estimated CrCl <70 ml/min, n/N (%)	128/215 (59.5)	118/213 (55.4)	[redacted]	[redacted]
Binet stage A B C	 21.3 35.6 43.1	 20.4 37.0 42.6	[redacted]	[redacted]
ECOG PS 0 1 2 3	 41.2 45.8 12.5 0.5	 47.9 40.5 11.6 0	[redacted]	[redacted]
Cytogenetic subgroup, n/N (%) by the hierarchical model of Döhner et al [14]				
Deletion in 17p	7.9[a]	6.5[a]	[redacted]	[redacted]
TP53 mutational status, Mutated, n/N (%)	[redacted][b]	[redacted]	[redacted]	[redacted]
Del(17p)/TP53 mutation Non-del(17p)/TP53 mutation Missing	[redacted][ab]	[redacted][ab]	[redacted]	[redacted]
IGHV mutational status, mutated	35.2[c]	38.4[c]	[redacted]	[redacted]
Comorbidities % (frequently reported: >30% of patients overall; or imbalanced)				
Vascular disorders	[redacted]	[redacted]	NR	NR
Hypertension	[redacted]	[redacted]	NR	NR
Metabolism and nutrition disorders	[redacted]	[redacted]	NR	NR
Hypercholesterolaemia	[redacted]	[redacted]	NR	NR

Gastrointestinal disorders	[redacted]	[redacted]	NR	NR
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	NR	NR
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	NR	NR
COPD	[redacted]	[redacted]	NR	NR
Asthma	[redacted]	[redacted]	NR	NR
Psychiatric disorders	[redacted]	[redacted]	NR	NR
Insomnia	[redacted]	[redacted]	NR	NR

CIRS: cumulative illness rating scale; COPD: Chronic Obstructive Pulmonary Disease; CrCl: Creatinine Clearance; ECOG: Eastern Cooperative Oncology Group; NR, not reported; PS: Performance Status; TLS, tumour lysis syndrome. [a] Proportions calculated by ERG using N=216 rather than the N minus missing data as presented in the CS. [b] Values in the CS are incorrect, values here are from clarification response A4 and the CSR corrigendum. [c] CS Appendix Table 46 and CSR reports the proportion with missing data and/or not evaluable and correctly calculates the proportions using the total N in each arm (N=216); the proportions presented in CS Table 9 are different as the company uses the N minus missing data.

4.2.1 Non-RCTs

The CS does not include any non-RCTs. The ERG has identified that the results from the participants included in the run-in to CLL14 were published in a summary paper in 2017.[12] Eleven of the participants completed 12 months of therapy. The publication focus was on safety but response outcomes were also reported (see section 4.8 for participant characteristics and key results).

4.2.2 Ongoing studies

The CS refers to an ongoing study of VenG. The CLL13 trial (NCT02950051) is a multi-centre four-arm RCT that has recruited 926 participants. The clinical trial record states the study is active and that the primary completion date is January 2023. The trial compares standard chemotherapy (FCR or BR) with VenG, venetoclax plus rituximab or triple therapy of VenG plus ibrutinib. The two co-primary outcomes are MRD negativity in peripheral blood and PFS. The population is previously untreated and meets the NICE scope, but does not meet the CS decision problem as participants are physically fit CLL patients (CrCl ≥70ml/min; CIRS ≤ 6; comorbidities excluded). The study is only including participants without del(17p) or TP53 mutation. The ERG have identified one publication summarising the key methods of the CLL13 trial in a conference abstract.[15]

The ERG's searches did not identify any other relevant ongoing studies.

4.3 Description and critique of company's outcome selection

The CS presents all outcomes specified by the NICE scope [overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment and health-related quality of life (HRQoL)] from the CLL14 trial. Additional outcomes measured in CLL14 and presented in the CS are minimal residual disease (MRD); duration of response (DOR); event-free survival (EFS) and time to next [anti-leukemic] treatment (TTNT). Safety outcomes were also reported in the CS. These outcomes are summarised in CS Table 7 and the reliability, validity and current use of each outcome in CS Table 8.

Investigator assessed PFS was the primary outcome measure in the trial. PFS was defined as time from randomisation to the first occurrence of progression, relapse, or death from any cause. The International Workshop CLL criteria[11] for PFS were used.

PFS by independent review committee (IRC) was a secondary outcome measure. This used the International Workshop CLL criteria[11] and included at least three experts who were blinded to treatment arm and investigator assessment of response. The investigator assessed and IRC assessed PFS results were similar, with a slightly more favourable hazard ratio (HR) with the IRC assessments (both presented in section 4.4). The latter was used in the CS economic model (section 5.2).

Other secondary outcomes were:

- Overall response rate (ORR), defined as the proportion of participants with a complete response (CR), a complete response with incomplete bone marrow recovery (CRi) or partial response (PR), assessed by the investigator as per International Workshop CLL criteria.[11] ORR was assessed at treatment end and at end of combination treatment assessment (Cycle 7, Day 1 or 28 days after last intravenous infusion), although the latter timepoint was not presented in the CS.
- A composite outcome of CR or CRi at completion of treatment as per International Workshop CLL criteria.[11] The ERG clinical advisor agrees this is a clinically important outcome.
- MRD response rate, defined as the proportion with undetectable MRD in peripheral blood and in bone marrow at completion of treatment and at completion of combination treatment (Cycle 9, Day 1 or 3 months after last IV infusion), although the latter timepoint was not presented in the CS. Undetectable MRD was measured by Allele-

specific oligonucleotide polymerase chain reaction (defined as having < 1 CLL cell per 10,000 leukocytes in peripheral blood or bone marrow). The ERG clinical advisor confirms that undetectable MRD is an important surrogate endpoint, particularly in bone marrow, and that there is a relationship between undetectable MRD and final outcomes in CLL. The CS (B.1.3.3) reports evidence that undetectable MRD leads to improved PFS in CLL and that the European Medicines Agency (EMA) has included undetectable MRD as an intermediate endpoint in recent guidelines for the evaluation of cancer treatments.[16, 17] However, a recent review argues that while MRD status has been shown to be a predictor of PFS and OS following chemo-immunotherapy, data for the relationship between MRD and outcomes following venetoclax are only emerging and need further validation.[18] MRD is not a NICE scoped outcome and has not been used as an outcome in the economic models of previous technology appraisals for CLL. Table 5 of the CS states that MRD outcomes were used in the CS economic evaluation, although there is no explicit description of this in the economic section and the company confirmed at clarifications that this was an error in Table 5 (A18).

- Overall survival was defined as the time from randomisation to death due to any cause. Data were immature at the time of the current analysis. The company clarified that overall survival was used in the economic model, despite CS Table 5 suggesting that it was not (clarification response A18).
- DOR which was defined as time from the first occurrence of a documented overall response to the first occurrence of progression or relapse as determined by the investigator or death from any cause.
- Event-free survival, defined as time between date of randomization and the date of investigator-assessed disease progression/relapse, death, or start of a new anti-leukemic therapy.
- TTNT with an anti-leukaemic agent, which was defined as the time between the date of randomisation and the date of first intake of new anti-leukemic therapy or death from any cause. TTNT was used in the economic model.
- Patient reported outcome measures (PROs) including validated measures of HRQoL (EuroQol 5 dimensions [EQ-5D-3L]; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30]) and symptoms (M.D. Anderson Symptom Inventory-CLL [MDASI-CLL]). HRQoL was explored in a scenario in the economic model (clarification response A18).

- Safety, including adverse events and serious adverse events, vital signs, lymphocyte immunophenotyping, premature withdrawals. Adverse effects were included in the economic model.

Exploratory outcomes were: (none of these are discussed further by the ERG)

- MRD (measured with different technologies and using different cut-offs)
- Relationship between blood MRD and PFS
- Relationships between baseline markers and clinical outcomes.

The CS reported all outcomes stated in the protocol and NCT record, although selected timepoints were reported for some outcomes.

4.4 Summary and critique of company approach to statistical analysis and results

4.4.1 Company submissions

The company provided data to the ERG in the following four submissions:

- The original CS and CSR: data-cut August 2018 (28.1 months median follow-up)
- The clarification responses and CSR Corrigendum: data-cut August 2018, correcting errors in the original CS Figure 15 for subgroup analysis of del(17p)/TP53 mutation
- The CS addendum and CSR Supplement: data cut August 2019 (39.6 months median follow-up)
- The CS addendum clarification responses: data-cut August 2019

In the original CS, the company presents multiple outcomes from the CLL14 trial which are consistent with the outcomes specified in their trial protocol.[7] These results are for the whole trial population, unless specified, hence combining patients with and without del(17p)/TP53 mutation. The August 2018 data-cut presented in this submission was not the originally planned primary analysis point, which was scheduled for when 170 PFS events had occurred. Instead, the analyses used the data from the planned interim analysis which was conducted when 65% of the planned PFS events (n=107) had occurred. The interim analysis was originally planned for when 75% of PFS events (n=128) had occurred. The change was based on recommendations from the trial's independent data monitoring committee through a protocol amendment

(version 7) which describes why the interim analysis was performed earlier than originally planned. Hence, these data are very immature and it is not possible to draw conclusions for all of the specified outcomes. This is particularly problematic when it comes to extrapolation performed in the cost-effectiveness section.

In the CS addendum, key outcomes analysed at the August 2019 data-cut are presented. This data cut excluded response measures (which were only assessed at end of treatment) and IRC assessed PFS. A total of [redacted] investigator-assessed PFS events had been observed, still fewer than the number planned for the original primary analysis point. For OS and TTNT, [redacted] and [redacted] events were observed respectively. PROs are not presented in the CS addendum but are available in the updated CSR supplement.

4.4.2 Summary of trial statistics

In the original CLL14 protocol, the company states that analyses would be stratified only by Binet stage. However, the company states that the analyses in their submission are stratified by Binet stage and geographic region (both were stratification factors at randomisation), which is consistent with later versions of the protocol. The reason for this deviation is unclear, but it is not expected to have unduly influenced the results.

The ERG is otherwise satisfied that the analyses based on CLL14 performed by the company are statistically robust and that each analysis was performed on the most relevant population (i.e. ITT or Safety). The trial was well designed and suitably powered to answer its primary hypothesis.

4.4.3 Summary of trial results

A summary of key outcomes from the August 2018 data-cut, or the August 2019 data-cut where available, can be seen in Table 4.

Table 4 Summary of key outcomes

Outcome (95% CI)	VenG (n=216)	GCib (n=216)
Primary outcome: Investigator Assessed PFS (August 2019 data-cut)		
1 year PFS	[redacted]	[redacted]
2 year PFS	88.17 (83.72, 92.61)[a]	64.58 (57.95, 71.20)[a]
3 year PFS	81.9[redacted]	49.5[redacted]
Median PFS	Not reached	35.6[redacted]

	HR 0.31 (0.22, 0.44), p<0.0001	
Secondary outcomes (August 2018 data-cut except where stated)		
1 year PFS, IRC assessed 2 year PFS, IRC assessed	[redacted] (91.50, 97.71)[a] 88.59 (84.20, 92.98)[a]	[redacted] (87.27, 95.06)[a] 63.70 (56.99, 70.42)[a]
	HR 0.33 (0.22, 0.51), p<0.0001	
ORR at EOT	84.7% (79.22, 89.24)[a]	71.3% (64.77, 77.23)[a]
	Difference: 13.43 (5.47, 21.38), p=0.0007[a]	
CR and CRi at EOT	49.5% (42.68, 56.40)[a]	23.1% (17.70, 29.35)[a]
	Difference: 26.39 (17.41, 35.36), p<0.0001[a]	
DOR (August 2019)	HR: [redacted]	
TTNT (August 2019)	HR: 0.51 (0.34, 0.78), p=0.0012	
MRD-Negative blood at EOT	75.5%	35.2%
	Difference: 40.3 (31.5, 49.1), p<0.001	
MRD-Negative bone marrow at EOT	56.9%	17.1%
	Difference: 39.8 (31.3, 48.4), p<0.001	
MRD-Negative blood at 18 months post treatment (August 2019)	47.2	7.4
	[redacted]	
OS (August 2019)	HR 1.03 (0.60, 1.75), p=0.921	
EFS (August 2019)	HR [redacted]	

[a]From FDA report [19]

CR: Complete response: CRi: Complete response with incomplete bone marrow recovery; DOR: Duration of Response; EFS: Event free survival; EOT: End of treatment assessment (3 months); HR: Hazard ratio; IRC: Independent Review Committee; MRD: Minimal residual disease; OS: Overall survival; PFS: progression free survival'; TTNT: Time to next (anti-leukaemic) treatment

4.4.4 Progression-free survival

The primary outcome was investigator assessed progression-free survival (PFS). At the most recent data-cut (August 2019) with a median follow-up of 39.6 months, VenG demonstrated superior efficacy on this outcome, with a hazard ratio of 0.31 (95% CI: 0.22, 0.44; p<0.0001). The company does not present an analysis of whether the hazard ratio, which assumes proportionality of the hazard rates between the two trial arms, is a suitable outcome when reporting this result. However, in their cost-effectiveness section, the company concludes that proportionality is not held. This would suggest that the estimate of the hazard ratio is not an accurate representation of the benefit of VenG on PFS. Despite this concern, the magnitude and statistical significance of the benefit, alongside the visual difference in the treatments on the Kaplan Meier plots (CS Figure 3 and CS addendum Figure 2) mean that the ERG accepts that there is clear and meaningful benefit of VenG over GClb for the primary outcome. Median PFS was not reached in the VenG arm and was 35.6 months (95% CI: 33.7, 40.7) in the GClb arm.

An independent review committee also assessed PFS at the August 2018 data-cut (but not the 2019 data-cut). The results were almost identical to the most recent data cut (investigator-assessed), with a reported hazard ratio of 0.33 (95% CI: 0.22, 0.51; p<0.0001).

4.4.5 Response Rates

Complete and partial response (CR, PR) were assessed in line with the International Workshop on CLL standards[11] and were assessed at the pre-specified end of treatment assessment, conducted 3 months after a patient received their last treatment dose. These outcomes were therefore not updated at the August 2019 data-cut. The company also included in their analysis a complete response with incomplete bone marrow recovery (CRi). The company only present a formal analysis of CR and CRi combined, which demonstrated a 26.4% higher response rate for patients on VenG (95% CI 17.4%, 35.4%; p<0.0001).

A comparison of the PR rates show a lower rate for VenG than GClb (35.2% vs 48.1%), however this may be explained by the higher CR/CRi rate of VenG (49.5% vs 23.1%).

4.4.6 Minimal Residual Disease

Minimal residual disease (MRD, see section 4.3) was measured in both blood and bone marrow of patients at cycle 9 and at 3 months following a patient's last treatment dose. Additional assessments of blood measurements were made at baseline, cycle 7, cycle 12 and every 3 months following end of treatment. There was also an end of treatment (EOT) assessment which occurred 3 months after treatment completion/early termination (Addendum clarification response A3 explained that this was different to the follow-up month 3 assessment). MRD response rate was determined as the number of patients achieving MRD negativity. The main secondary outcome was rate of MRD negativity in blood at the EOT assessment. The company reports that VenG achieved 75.5% MRD negativity compared to 35.2% in the GClb arm at the EOT measurement. At the 18 month post-treatment follow-up (August 2019 data-cut), both arms showed decreased levels of MRD negativity. The company reports 47.2% negativity for VenG and 7.4% for GClb.

A separate assessment of marrow measurements was also undertaken, which at 3 months post-treatment showed lower rates of negativity for both arms than the blood measurements. Here, VenG achieved negativity in 56.9% of patients, compared to 17.1% of patients on GClb. No additional bone marrow assessments were undertaken after this.

The company report that the level of agreement between the two measures at three months post-treatment was high for the VenG arm, however the degree of missing bone marrow measurements makes this difficult to conclude. Whilst agreement of paired measurements for the VenG arm was high at [redacted], it was lower for GClb ([redacted]) suggesting blood measurements of MRD negativity may not be a suitable replacement for bone marrow. The company also performed an analysis of MRD negativity among patients with a CR where the results showed continued benefit of VenG (although note the data presented in CS Table 18 were incorrect, confirmed in clarification response A8). It is also clear that the majority of cases where MRD negativity is achieved are not sustained, for either arm. This could suggest that there is some waning of effect of VenG.

Additionally, the company presents output from an analysis where Kaplan-Meier curves are presented for PFS, but are stratified by treatment arm and MRD negativity status. Whilst no conclusions can be drawn due to a lack of formal hypothesis testing there appears to be a trend demonstrating that MRD negativity from either blood or bone marrow is associated with improved PFS survival. It is apparent that in both arms some patients have a PFS event after having achieved MRD negativity, though it is unclear whether this is disease progression or death.

4.4.7 Overall survival

Overall survival (OS) was a secondary outcome of the CLL14 trial. At the most recent data-cut (August 2019), [redacted] deaths had occurred in both groups (CS Addendum). The hazard ratio for overall survival at the August 2019 data-cut is 1.03 (95% CI: 0.60, 1.75), suggesting that there is no difference in overall survival between VenG and GClb, although there is a degree of uncertainty around the estimate. No assessment of proportional hazards was made alongside the company's presentation of the hazard ratio, but in their cost-effectiveness section the company accept the assumption based on the limited follow-up from CLL14.

4.4.8 Duration of Response

The duration of objective response (DOR) was defined as the time from the first occurrence of a response until a time of disease progression or death. A total of 197 responders to GClb and 200 responders to VenG were included in the analysis. The company described how these numbers were calculated in clarification response A9. There were 60 additional responders in this

analysis (43 from the GClb arm, and 17 from the VenG arm) who had an investigator assessment of response at any time during the study other than for the EOT assessment. These 60 patients were not included in the ORR calculation at EOT. The company again modelled a hazard ratio which assumed proportional hazards without verification of the assumption of proportionality. The ERG believes the assumption is likely to be violated given that the DOR curves for the two arms are identical for the first 10 months before separating. Despite this, at the August 2019 data-cut the stratified hazard ratio of DOR was [redacted]) and the separation of the Kaplan-Meier curves indicates a superior DOR in favour of VenG. This is unsurprising as the responses to VenG were more likely to be a complete response rather than a partial response, compared to GClb.

4.4.9 Event-free survival

Event-free survival (EFS) was defined as the time from randomisation until disease progression or relapse, death or the start of the new anti-leukemic therapy. The company again presents a hazard ratio without consideration of the assumptions made. The analyses were based on [redacted] EFS events on VenG and [redacted] EFS events on GClb. Whilst there was little to distinguish between the Kaplan-Meier curves for the first 12 months of follow-up, the curves did separate beyond this point, in favour of VenG. The hazard ratio of [redacted]) at the August 2019 data-cut indicates that the rate of EFS events was lower on VenG. The events in this analysis are dominated by PFS events, and hence the results are almost identical to those for the PFS outcome.

4.4.10 Time to next treatment

The company defined time to the next anti-leukemic treatment (TTNT) as the time between the date of randomisation and the date of a patient receiving a second line therapy. The original CLL14 trial protocol[7] states "Patients who have not taken new anti-leukemic therapy will be censored at their last assessment prior to the analysis or date of death". However, in their submission it is clear that the company treat death as events in the TTNT analysis, rather than as censored observations, which is consistent with later versions of the protocol.

It is unclear to the ERG how the inclusion of OS events confounds this analysis, in terms of both the magnitude and the statistical significance of the hazard ratio, as the OS events are indistinguishable from the true next treatment events. It is potentially incorrect to include OS

events in the analysis, as the reader infers that that a patient has begun second line therapy when they are actually no longer alive.

Aside from this, the company reports a hazard ratio of 0.51 (95% CI: 0.34, 0.78; p = [redacted]) at the August 2019 data-cut, suggesting that VenG has a significantly lower hazard rate of next treatment or death events than GClb. Evidence from the previous data-cut suggested that the assumption of proportional hazards for TTNT was violated, which is consistent with the crossing Kaplan-Meier curves for the most recent data cut. This casts further doubt on the suitability and interpretability of the hazard ratio reported by the company for this outcome.

The ERG requested an analysis of the TTNT outcome where death events were censored instead of counted as discrete events. In the addendum clarification response B10, the company presented a hazard ratio of [redacted], but without confidence intervals or test of statistical significance. This limited information further supports the conclusion that VenG does delay the TTNT, relative to GClb.

4.4.11 Unreported trial outcomes

Overall response rate at the completion of combination treatment assessment was also reported as a secondary outcome in the CLL14 protocol. This was due at the start of cycle seven or a month after a patient's last intravenous infusion. However, the company have not presented the results for this outcome in their submission, or in the published manuscript of this trial. Whilst the related outcome of response rate at the end of treatment assessment has been reported, it is concerning to see any secondary outcome omitted. The results were in the original CLL14 CSR (data-cut August 2018), which did not indicate a significant difference between treatments. The response rate for GClb was [redacted] and for VenG was [redacted].

In their protocol the company also included a consideration of the MRD response rates in the peripheral blood and in marrow at the completion of combination of treatment assessment, which was due this time at the start of cycle 9 or 3 months after a patient's last intravenous infusion. These results were also omitted from the company submission, but were identified in the original CSR (data-cut August 2018). For peripheral blood at cycle 9, [redacted] of GClb patients were MRD negative compared to [redacted] of VenG patients. For marrow, the proportions were lower for both arms, with GClb achieving MRD negativity in [redacted] of patients, and VenG in [redacted] of patients.

4.4.12 Patient reported outcomes

The company utilised three questionnaires that captured patient quality of life on various scales across the duration of the trial (EQ-5D-3L, MDASI-CLL and EORTC QLQ-C30). The results for each specific assessment can be found in Appendix L of the CS and in more detail in clarification response A10, but in summary, all showed a [redacted] from baseline score, which [redacted]. The company does not report what the baseline values were.

These results [redacted] in terms of change from baseline between the arms of CLL14 at any point in the follow-up. Although the company did not present updated analyses of PROs in their Addendum for the August 2019 data-cut, data in the updated CSR demonstrate that [redacted] This is [redacted] given the observed benefit of VenG, ensuring patients remain progression-free for longer, which is generally associated with a better quality of life. Whilst it is difficult to conclude what may be influencing this [redacted] result, [redacted]

4.4.13 Subgroups

The company presents results of pre-specified subgroup analyses on investigator assessed PFS. The analyses can only be considered exploratory as they were not accounted for in the power calculation and no formal tests of interaction with treatment effect were performed.

There is a discrepancy between the types of subgroups reported in the original CS and the Addendum. Age (<75 vs ≥75), gender (male vs female) and Binet stage (A vs B vs C) were reported only in the original CS (despite the table and text of the Addendum referring to these subgroups). At the August 2018 data-cut, whilst there was a trend of higher relative efficacy of VenG in patients with lower Binet stage, there was consistency across age group and gender (CS Figure 15).

The CS Addendum Figure 8 presents subgroup analyses for TP53 mutation status (mutated, unmutated, unknown) and presence of del(17p), but not the combined subgroup of del(17p)/TP53 mutation presented in CS Figure 15 and defined in the Decision Problem of the

original CS (although the company noted in clarification A4 that there is an error in the del(17p)/TP53 mutation subgroup in CS Figure 15 and provided corrected analyses for the August 2018 data-cut). In response to Addendum Clarification question A1, the company provided investigator assessed PFS by del(17p)/TP53 mutation status at the August 2019 data-cut, see Table 5.

Table 5 Investigator-assessed PFS according to del(17p)/TP53 mutation status, August 2019 data-cut

Subgroup	VenG		GClb		Hazard ratio (95% CI)
	n	Median, months (95% CI)	n	Median, months (95% CI)	
Non-del (17p)/TP53 mutation	184	[redacted]	184	[redacted]	[redacted]
Del(17p)/TP53 mutation	25	[redacted]	24	[redacted]	[redacted]
Undefined mutation status	7	[redacted]	8	[redacted]	[redacted]

NE, not evaluable.

In CS Addendum Figure 8, updated data for IGHV mutational status and cytogenic subgroups are presented. Additional pre-specified subgroups of serum Beta2-microglobulin category, ECOG status, and time from diagnosis to randomisation were also presented. There is consistency of treatment effect across these subgroups.

In the CLL14 protocol, the company specified a further nine subgroups that would be investigated, but are not included in their submission: geographic region, B-symptoms, age (continuous), age (additional categorisations), race, ethnicity, TLS risk, CIRS score and creatinine clearance.

4.5 Critique of trials identified and included in the indirect comparison

Ibrutinib comparator studies

The company identified three studies (Mato 2018,[20] Ahn 2018,[21] ALLIANCE[22]) that could be used to indirectly compare VenG with ibrutinib for people with previously untreated CLL and del(17p)/TP53 mutation. One of these studies, ALLIANCE,[22] was excluded due to the small sample size of the relevant subgroup (n=9). After conducting a feasibility assessment, the company selected Mato 2018 as the preferred study due to its larger sample size, with a secondary comparison using Ahn 2018 presented in CS Appendix D.1.4.

The three ibrutinib studies identified by the company are discussed below.

As noted in section 4.2, the numbers, baseline characteristics and results of patients with TP53 mutation and del(17p)/TP53 mutation in the CS and CSR of CLL14 are incorrect, therefore the company provided corrected baseline characteristics and results in clarification response A4; these are presented in Table 6 below.

Mato 2018

Mato 2018[20] is a retrospective observational cohort study of people with CLL treated with ibrutinib in the front-line setting (see Table 6 for a comparison of study details). Information was obtained from chart review, electronic medical records and related databases. Patients were categorised according to age (< 65 years or ≥ 65 years) and presence or absence of del(17p). These reflect the key inclusion criteria of the pivotal RESONATE-2 RCT of ibrutinib in patients with untreated CLL or small lymphocytic lymphoma (SLL) *without* del(17p) and aged 65 years or over.[23] Mato 2018 also categorised patients separately according to presence or absence of TP53 mutation. The CS is not clear on this point, referring to the relevant subgroup of patients in the Mato 2018 study (n=110) as having del(17p)/TP53 mutation, when in fact their TP53 status is unknown. The ERG notes that the Kaplan-Meier plot for PFS includes 108 del(17p) patients rather than 110, the reason for this is not reported. The ERG also notes that the Mato 2018 whole population contained an additional 8 patients who had TP53 mutations without del(17p) who were not included in the subgroup analysed; these patients are relevant to the current appraisal.

Co-existing conditions with a CIRS score >6 or CrCl < 70ml/min, as required by CLL14, were not reported in Mato 2018, so it is unclear whether the populations were comparable in this respect. Moreover, baseline characteristics were not presented for the subgroup with del(17p). In CS section B.2.9.3, the CS correctly states that the Mato 2018 publication included all ages (whole population n=391, median age 68 years, range 32-96 years, 41% <65 years), although the ages in the relevant del(17p) subgroup are unknown. The CS also states that the CLL14 trial only included patients aged ≥65 years and that '*the inclusion of younger patients in the Mato et al. study could drive the results of the relative comparison to the CLL14 data and generate a trend of ibrutinib superiority*' (CS B.2.9.3). However, the ERG notes that [redacted] of the CLL14 del(17p)/TP53 mutation subgroup were less than 65 years. In response A27 the company clarified that the statement in the CS: 'the CLL14 trial only included patients aged 65 years and above' is incorrect. The median age of the CLL14 whole trial population was 72 years, with [redacted] <65 years.

Overall, the ERG considers that comparability of the Mato 2018 del(17p) subgroup with the CLL14 del(17p)/TP53 mutation subgroup cannot be ascertained. However, based on the characteristics of the whole populations, it is likely that the patients in the Mato 2018 subgroup are younger and fitter. A summary of key results is presented in Table 7.

Ahn 2018

Ahn 2018[21] reports 5-year follow-up of a single arm phase 2 study of ibrutinib in untreated or relapsed/refractory CLL or SLL. Two cohorts are reported: those with age ≥65 years (not relevant as few had del(17p)/TP53 mutation) and those with del(17p)/TP53 mutation. Previous results were published in Farooqui 2015,[24] which was considered in TA429[25] of ibrutinib. In TA429, evidence from Farooqui 2015 was presented for the untreated del(17p) or TP53 mutation population (n=35) but was not used to estimate clinical efficacy as data from the previously treated population were preferred by the company (Committee discussion: *The committee also noted that the single-arm Farooqui et al. (2014) study of ibrutinib presented by the company included a few patients with untreated CLL with a 17p deletion, but that the company did not use this to estimate clinical efficacy. The committee agreed that, in the absence of any evidence, the data from the previously treated population could be taken into account, but recognised this was associated with uncertainty.*)

CS Table 25 summarises baseline characteristics for the del(17p)/TP53 mutation subgroup (n=51) from Ahn 2018, however this includes both untreated (n=35, n=34 in analysis) and relapsed/refractory (n=16) patients with CLL. The company acknowledges this in clarification response A11. CS Appendix Table 9 states that the number of 'previously untreated CLL patients treated with ibrutinib with *TP53* aberrations' is 51, however this is incorrect. Some baseline characteristics for the relevant untreated del(17p)/TP53 mutation subgroup (n=35) are reported by the earlier publication,[24] but there are only three characteristics in common between the studies (age, sex and IGHV mutation) and there is no information on co-existing conditions or CRIS score. The Ahn 2018 subgroup was slightly younger and had fewer men than the CLL14 subgroup. CS page 65 states: '*Farooqui et al. reported on patients with previously untreated CLL patients with TP53 and del(17p), while the Ahn et al. reported on the CLL patients with TP53 aberrations'.* However, the ERG notes that '*TP53 aberrations'* in Ahn 2018 refers to del(17p) or TP53 mutations and, when stratified by treatment status, the untreated subgroup of Ahn 2018 is the same subgroup of patients reported in Farooqui 2015.

CS Appendix D.1.4 states patients without del(17p)/TP53 mutation were excluded from the indirect comparison, reducing the sample size of the population of interest to 24 for the VenG arm from the CLL14 trial and 18 for the ibrutinib arm from Ahn 2018, and that data sources were restricted to elderly patients (65 years and above) only. Clarification response A26 states

that this is incorrect, and that the correct sample size included in the analysis for Ahn 2018 is 34.

Overall, the ERG considers that there are a number of inaccuracies in the description of the Ahn 2018 study by the CS. The comparability of the Ahn 2018 untreated del(17p)/TP53 mutation subgroup with the CLL14 del(17p)/TP53 mutation subgroup cannot be clearly ascertained, although the Ahn 2018 subgroup is younger, has fewer men and is likely to have fewer comorbidities.

ALLIANCE

ALLIANCE[22] is a phase 3 RCT of ibrutinib, ibrutinib + rituximab, and bendamustine + rituximab in people with untreated CLL and age ≥65 years. In the ibrutinib arm, 9 patients had del(17p) and PFS is reported for this subgroup (also 15 patients had TP53 mutation, but results are not presented separately). This study was excluded by the company due to sample size <10. Baseline characteristics are not reported for the subgroup with del(17p) and there is no information on comorbidities or CIRS score. However, as trial participants were randomised to (and therefore suitable for) BR (bendamustine + rituximab) treatment, they are not comparable with the population in CLL14 (unsuitable for BR). This could be considered reasonable justification for exclusion of ALLIANCE from the indirect comparison, however given the lack of appropriate evidence and limitations with the other two studies, the ERG considers that analysis should have been undertaken. This was provided by the company in response to clarification A23.

Feasibility assessment

The ERG agrees that the absence of a common comparator between VenG and ibrutinib precludes an anchored comparison. The company conducted a feasibility assessment to determine the suitability of the available data for conducting an unanchored matching adjusted indirect comparison (MAIC), and concluded that it would not be feasible to conduct a MAIC. After examining the studies, the ERG agrees with this conclusion based on data published in ibrutinib studies. The company stated that unsuccessful attempts were made to contact the authors of the publications (clarification response A25). The ERG contacted the authors of these studies to request baseline data and individual patient data for the relevant subgroups and received a positive response from the ALLIANCE study. However, at the time of writing this report it is unclear whether data will be provided within the timelines of the current appraisal.

ERG summary: Three relevant studies of ibrutinib reported a subgroup of patients with previously untreated CLL and del(17p)/TP53 mutation. The studies did not report comorbidities or CIRS, therefore similarity to CLL14 in this respect could not be ascertained. Baseline characteristics of the relevant subgroups were not reported, therefore MAIC was not possible and comparability with the CLL14 del(17p)/TP53 mutation subgroup is uncertain. There is heterogeneity between these studies and CLL14 in the study designs, eligibility criteria, outcomes and unknown heterogeneity in baseline characteristics. In addition, some of the participants in the CLL14 trial subgroup may have been ineligible for ibrutinib due to cardiac disorders at baseline (clarification A15).

Table 6 Comparison of ibrutinib study details

	CLL14[a]	**Mato 2018**[20]	**Ahn 2018**[21] **(Farooqui 2015**[24]**)**	**ALLIANCE**[22]
Design	RCT	Retrospective observational cohort study	Single arm phase 2 study	RCT
Eligibility criteria	• Age ≥18 years • Life expectancy > 6 months • Previously untreated CLL • Total CIRS score >6 or CrCl <70 mL/min • CrCl ≥ 30 ml/min	• Previously untreated CLL • Treated with ibrutinib	• CLL or SLL • del(17p) or TP53 mutation for the TP53 cohort [*or* age ≤65 for elderly cohort] • ECOG PS ≤2 • Creatinine <2.0 mg/dL or CrCL 50 mL/min or less • Previously untreated CLL or R/R CLL	• Age ≥65 years • Previously untreated CLL • Intermediate or high-risk Rai stage CLL • ECOG PS ≤2
Relevant subgroup	**del(17p)/TP53 mutation: 25** del(17p): 17 TP53 mutation: 23	**del(17p): 110 (108 in analysis)** TP53 mutation: 44 Both del(17p) and TP53 mutation: 35[b] TP53 mutations without del(17p): 8	**del(17p)/TP53 mutation: 35 (34 in analysis) untreated**	**del(17p): 9 (untreated)** TP53 mutation: 15
Baseline characteristics reported by more than one study				
	VenG (n=25)	Ibrutinib (n=108)	Ibrutinib (n=35)	Ibrutinib (n=9)
Age	[redacted]	Not reported	median 62 (range 33‑82)	Not reported
% male	[redacted]	Not reported	66%	Not reported
IGHV un-mutated	[redacted]	Not reported	63%	Not reported

[a]baselines as reported in clarification response A4. [b] States 34 in results section.

Table 7 Key results in subgroup with untreated del(17p) and / or TP53 mutation (studies in indirect comparisons)

	CLL14 VenG (n=25)[a]	**Mato 2018[20] Ibrutinib (n=108)**	**Ahn 2018[21] (Farooqui 2015[24]) Ibrutinib (n=34)**	**ALLIANCE[22] Ibrutinib (n=9)**
ORR	NR	82.3% Both del(17p) and TP53 mutation (n=34): 91%	NR	NR
CR	NR	Clinical CR 21.2%	12%[b]	NR
PR	NR	43.5%	70%[b]	NR
PR with lymphocytosis	NR	17.6%	15%[b]	NR
SD	NR	13.0%	-	NR
PD	NR	4.6%	3%[b]	NR
Discontinuation rate	NR	33%	NR	NR
Mean time to discontinuation	NR	6.25 months	NR	NR
PFS	2 year: [redacted]%[a]	1 year: 87%	5 year: 74.4% (95% CI 60.2, 92.1)	2 year: 75%[c]
OS	1 year: [redacted][a]	n=103 1 year: 89%	5 year: 85.3% (95% CI 74.2, 98.1)	NR

[a]Results from clarification response A4 ([redacted]), August 2018 data-cut. [b]best response at 24 months follow-up. [c] estimated from Kaplan-Meier curve. NR, not reported.

4.6 Critique of the indirect comparison

In the absence of direct evidence, the company sought to perform an indirect comparison of VenG with ibrutinib for patients with del(17p)/TP53 mutation. In the CLL14 trial, there were just 25 patients with del(17p)/TP53 mutation who experienced [redacted] PFS events (August 2019 data-cut). The numbers of relevant patients in the comparator trials are 108 (Mato 2018.[20]), 34 (Ahn 2018 [21]) and 9 (Woyach 2018[22]) meaning any comparison would likely be considerably underpowered. When combined with previously discussed issues of heterogeneity, any comparison made will be extremely limited in its validity.

The company concluded that a MAIC was not suitable given the lower number of patients that would be eligible from CLL14 based on matching to the ibrutinib trial inclusion/exclusion criteria, even before matching to specific covariates. A MAIC is useful when you have access to patient level data from one trial, and apply weights to each patient such that the distribution of key population level variables match that of an arm of a target trial. Matching typically reduces the final overall sample size by reducing the weight of certain participants who do not match well to the target population. Hence, the ERG accept that a MAIC analysis would not be ideal, but

requested that the company attempt it given the heterogeneity present in the studies that may bias a naïve treatment comparison.

In their original submission, the company performed a naïve treatment comparison, which did not make any covariate adjustment and assumed the ibrutinib trials contained patients homogenous to those in the del(17p)/TP53 VenG population of CLL14. Clearly, this contains a number of significant risks, and the ERG advises that no conclusion should be drawn from such an analysis. The company perform the comparison utilising hazard ratios, but without any assessment of whether these are a suitable scale to compare the treatments. Also, digitising graphs to obtain patient level data that is representative of the trial data, but not necessarily identical, which is another source of uncertainty within these comparisons. Updated analyses using the August-2019 data cut are presented in the CS addendum.

The company's first comparison is to Mato 2018. Fitting a Cox proportional hazard model to the data produced a PFS hazard ratio of 0.660 (95% CI: 0.270, 1.615; p = 0.363). The wide confidence intervals suggest no conclusion can be drawn even if the assumptions of the analysis were valid. Furthermore, it is likely that this effect size is capturing a combination of treatment effect and differences in prognostic factors.

Fitting another Cox model to the OS data produced a hazard ratio of 0.841 (95% CI: 0.301, 2.352; p=0.741). Again, this analysis did not provide any useful information to meaningfully estimate a relative effect on OS between VenG and ibrutinib in del(17p)/TP53 mutation patients.

A naïve comparison to the most relevant patients from the study of Ahn 2018 produced a hazard ratio of [redacted] (95% CI: [redacted], [redacted]; p=[redacted]) for PFS, favouring ibrutinib. The OS data yielded a hazard ratio of [redacted] (95% CI: [redacted], [redacted]; p=[redacted]), also in favour of ibrutinib but not significantly.

The ERG requested additional analyses which pooled the recreated data for the ibrutinib patients prior to obtaining hazard ratios. The results were similar with the single study analyses, with a PFS hazard ratio of [redacted] (95% CI: [redacted], [redacted]; p=[redacted]) and an OS hazard ratio of [redacted] (95% CI: [redacted], [redacted]; p=[redacted]) (CS addendum clarification response B7), however it is

not possible to conclude whether these results could be considered more reliable than the others.

In summary, these indirect comparisons are inadequate for providing any meaningful information on the comparison of VenG and ibrutinib for either PFS or OS in patients with del(17p) or TP53 mutation.

4.7 Adverse events

The safety-evaluable population was used for the safety analysis, this population was defined as participants who received at least one dose of any study treatment. There were 212 participants in the safety analysis population for VenG and 214 for GClb. The CS presents only adverse events that were defined as treatment-emergent adverse events (TEAEs), these were events not present at the start of study treatment or an event that was already present which worsened with study treatment.

Treatment exposure rates were presented in CS Section B.2.10.2 and are summarised by the ERG in Table 8. Data were not available for some of these categories and it is therefore difficult to compare between treatments across all factors. The median dose intensity rate of venetoclax in the VenG arm was [redacted] and the median dose intensity of chlorambucil in the GClb arm was 95.4% (range 4-111%). In both arms the median dose intensity of obinutuzumab was 100% (range 0-111%). The proportion of participants with drug interruption or reductions ranged from [redacted] for obinutuzumab to 43.3% for venetoclax in the VenG arm, and between 26.9% on chlorambucil and [redacted] on obinutuzumab in the GClb arm.

Table 8 Summary of treatment exposure rates in CLL14 (safety-evaluable population)

	VenG (n=212)	**GClb (n=214)**
Completion of treatment		
Both agents Single agent period	[redacted] Venetoclax: [redacted] Obinutuzumab: NR	NR Chlorambucil: NR Obinutuzumab: NR
Number of cycles, median (range) per agent	Venetoclax: NR Obinutuzumab[redacted]	Chlorambucil: [redacted] Obinutuzumab[redacted]
Median duration of exposure from first dose, months (range)	[redacted]	NR

	VenG (n=212)	GClb (n=214)
Median (range) dose intensity per agent (for venetoclax this is after reaching target dose)	Venetoclax: [redacted] Obinutuzumab: 100% (0-111%)	Chlorambucil: 95.4% (4-111%) Obinutuzumab: 100% (0-111%)
Median total cumulative dose per agent	Venetoclax: NR Obinutuzumab: [redacted] mg	Chlorambucil: NR Obinutuzumab: [redacted] mg
Reached target dose single agent, n/N	Venetoclax: [redacted] Obinutuzumab: NR	Chlorambucil: NR Obinutuzumab: NR
Dose modification (interruption or reduction) rate in those reaching target dose, % per agent	Venetoclax: 43.3% Obinutuzumab: [redacted]	Chlorambucil: 26.9% Obinutuzumab: [redacted]

[a] [redacted] did not reach the 400mg target dose for a variety of reasons, including AEs and withdrawal of consent. NR: Not reported (in the CS or CSR)

4.7.1 Overview of treatment-emergent adverse events

Table 9 provides a summary overview of the key rates of adverse events in CLL14 and these are described in more detail below. Adverse events (AEs) were collected until 28 days post-treatment, and grade 3-4 adverse events (other than grade 3-4 infections, which were reported for 2 years after the last dose) were collected until 6 months post treatment, therefore these were not updated in the August 2019 data-cut (although there are minor differences in the update due to data cleaning and administrative updates). Serious adverse events (SAEs) and fatal AEs were updated at the August 2019 data-cut.

TEAEs were experienced in [redacted]% of participants in the VenG arm and [redacted]% of participants in the GClb arm.

There are minor differences between data reported in the original CS (and trial publication,[7] VenG 78.8% vs GClb 76.6%) and the updated CSR supplement (VenG [redacted] vs GClb [redacted]) due to data cleaning or administrative updates. Corrected data from the CSR supplement are presented below where available. CS Addendum Table 12 also reports grade 3-4 adverse events 'at greatest intensity' of [redacted] with VenG and [redacted] with GClb.

At the August 2019 data-cut, SAEs were experienced in [redacted]% of participants in the VenG arm and [redacted]% of participants in the GClb arm. The all-cause death rate during the trial was similar between groups, however, deaths due to adverse events were higher in the VenG arm ([redacted]% vs [redacted]%) (Table 9). Treatment discontinuation rates (any treatment) were similar between arms.

Table 9 Summary of adverse events in CLL14, safety-evaluable population

%	VenG (n=212)	GClb (n=214)
Any treatment-emergent AE	[redacted]	[redacted]
Treatment-related grade 3-4 AE	[redacted]	[redacted]
Any treatment discontinuation for TEAE	14.6	15.9
At least one SAE (August 2019)	[redacted]	[redacted]
Death (any cause) (August 2019)	[redacted]	[redacted][a]
Death related to AE (August 2019)	[redacted]	[redacted]

[a] Excludes one participant who died prior to randomisation
AE: Adverse event, SAE: Serious Adverse event; TEAE: treatment-emergent adverse event.

4.7.2 Grade 3-4 adverse events

National Cancer Institute Common Terminology Criteria for Adverse Events were used to assess the severity of AEs.[7] The CS reports the grade 3-4 TEAEs that had a difference of at least 2% between treatment arms (coded using MedDRA v21.0) (CS Table 28) and those with an incidence of at least 1% in either arm because these were used in the CS economic evaluation (CS Table 29). Grade 3-4 TEAEs with at least 2% greater incidence in the VenG arm were neutropenia ([redacted] VenG versus [redacted]% GClb); hyperglycaemia (3.8% VenG versus 1.4% GClb); diarrhoea ([redacted] VenG versus [redacted] GClb August 2019) and hypertension ([redacted] VenG versus [redacted] GClb). Grade 3-4 leukopenia was more commonly experienced in the GClb group compared with the VenG group ([redacted] VenG versus [redacted] GClb). Neutropenia and diarrhoea are known adverse drug reactions related with venetoclax.

Key grade 3-4 TEAEs used in the CS economic model can be seen in Table 10; rates were higher in the VenG group for asthenia ([redacted] VenG) and dyspnoea ([redacted] VenG) versus GClb (both events [redacted]); febrile neutropenia ([redacted] VenG versus [redacted] GClb) and sepsis ([redacted] versus [redacted] GClb). The ERG notes that sepsis has a difference of greater than 2% between groups.

Table 10 Grade 3-4 TEAEs used in the CS economic evaluation (updated CSR)

%	VenG (n=212)	GClb (n=214)
Asthenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Sepsis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]

4.7.3 Serious adverse events and deaths

SAEs were defined as any adverse event that is fatal, life threatening, requires or prolongs hospital stay, results in persistent or significant disability/incapacity, any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug or any other significant medical event.[7] As seen in Table 9 above, SAEs were experienced in more participants ([redacted]%) in the VenG arm than in the GClb arm ([redacted]%) at the August 2019 data-cut. The company did not provide details of SAEs for the treatment and post-treatment phases of the trial combined. The ERG has therefore presented SAEs (experienced by at least 1% of participants in at least one arm of the CLL14 trial) reported in the post-treatment period (from CS Addendum Table 13) alongside those reported during the treatment phase of the trial (shown in Table 11). The most frequently reported SAEs in the VenG arm at the August 2018 data cut were febrile neutropenia, pneumonia, infusion-related reaction and pyrexia. These were also the most frequently reported SAEs in the GClb arm and of these only febrile neutropenia (higher for VenG) and infusion-related reactions (higher for GClb) had a ≥1% difference between groups. Overall there were no SAEs that were experienced ≥2% more in one of the groups.

Table 11 Summary of SAEs with ≥1% incidence in either treatment group

	August 2018 data cut		**Post treatment period, August 2019 data cut**	
%	**VenG (N=212)**	**GClb (N=214)**	**VenG (N=202)**	**GClb (N=208)**
Pneumonia	4.7	4.2	[redacted]	[redacted]
Sepsis	2.8	0.9	[redacted]	[redacted]
Cellulitis	1.4	0	[redacted]	[redacted]
Infusion-related reaction	4.2	6.1	[redacted]	[redacted]
Febrile neutropenia	5.2	3.7	[redacted]	[redacted]
Thrombocytopenia	0.9	2.3	[redacted]	[redacted]
Neutropenia	1.4	0.5	[redacted]	[redacted]
Squamous cell carcinoma	0.9	1.4	[redacted]	[redacted]
Pyrexia	3.8	3.3	[redacted]	[redacted]
COPD	1.4	0.9	[redacted]	[redacted]
Atrial Fibrillation	0.5	1.4	[redacted]	[redacted]
Cardiac Failure	1.4	0.5	[redacted]	[redacted]
Myocardial infarction	0.5	1.4	[redacted]	[redacted]
Tumour lysis syndrome	0.5	1.9	[redacted]	[redacted]
Aspartate aminotransferase increased	0	1.9	[redacted]	[redacted]
Alanine aminotransferase increased	0	1.4	[redacted]	[redacted]

COPD: Chronic Obstructive Pulmonary Disease. Additional SAEs occurring during the post-treatment period: respiratory tract infection, prostate cancer, cerebral ischaemia, dehydration, hypertension, vertigo (all VenG 1% vs GClb <1%, CS Addendum Table 13).

As described above, there were more deaths related to TEAEs with VenG (see Table 9). Sepsis / septic shock was the most frequently reported TEAE leading to death (participants in the VenG arm and in the GClb arm, August 2019 data-cut). The CS states that a causal association with venetoclax and death was unlikely because of the long latency period from the last dose of study drug (of deaths assessed in August 2018, 11 of the VenG arm died 29 days or more after last study drug), pre-existing medical conditions and concomitant comorbidities. The ERG notes that four of the eight participants in the GClb arm who had died as a result of TEAEs at the August 2018 data cut died in the post-treatment period and that participants in both arms had pre-existing medical conditions and concomitant comorbidities. Two of the deaths in the VenG arm at the August 2018 data cut were attributed a causal relationship to obinutuzumab by the investigator.

4.7.4 Adverse events of any grade

Table 12 provides a summary of specific adverse events with ≥10% incidence in either treatment group (reproduced from the Fischer publication of the CLL14 trial,[7] data-cut August 2018) for context. Events with a 5% or greater difference between groups are in bold.

Table 12 Overview of AEs with incidence of ≥10% in either group at August 2018

%	VenG (N=212)	GClb (N=214)
Neutropenia	57.5	57.0
Thrombocytopenia	24.1	23.4
Anaemia	16.5	18.7
Infusion-related reaction	**44.8**	**51.4**
Diarrhoea	**27.8**	**15.0**
Nausea	18.9	21.5
Constipation	13.2	8.9
Pyrexia	**22.6**	**15.4**
Fatigue	15.1	14.0
Cough	16.0	11.7
Headache	11.3	9.8

4.7.5 Tumour lysis syndrome

Tumour lysis syndrome is an important consideration in the treatment of CLL (section 4.2). At the August 2018 data-cut, TLS was reported in three VenG treated participants and in five GClb treated participants. All cases in the VenG arm occurred during treatment with obinutuzumab

and before treatment with venetoclax and none met the Howard criteria for clinical TLS; that is the presence of specific electrolyte changes and clinical manifestations.

4.8 Additional work on clinical effectiveness undertaken by the ERG

Updated searches for published and ongoing studies were undertaken by the ERG.

Eight new publications relevant to the submission were identified: two VenG studies[9, 12] (see section 4.8.1), one GClb study[26], one abstract linked to the ongoing CLL13 study[15] (see section 4.2.2) and four abstracts linked to CLL14.[27-30] The CLL14 abstracts were checked for additional data but none were identified. No ongoing studies were identified.

The two additional studies of VenG[9, 12] identified by the ERG are summarised here. In addition, the ERG has summarised the CLL11 trial[31], which is referred to by the company for external validation of the GClb arm, and the ERIC real-world study of GClb.[26]

4.8.1 Additional VenG studies

The results from the participants included in the run-in to CLL14 were published in a summary paper in 2017.[12] This was not reported by the CS.

Thirteen previously untreated CLL patients received VenG. The dose regimen was the same as for participants of CLL14 (section 4.2). Baseline characteristics of these participants are in Table 13.

Table 13 Baseline characteristics of CLL14 run-in participants

% unless stated	N=13
Median (range) Age ≥70 years	75.0 (59-88) 84.6
Male sex	61.5
Total CIRS score >6	76.9
Estimated CrCl <70 ml/min	76.9
Binet stage A B C	 15.4 23.1 61.5
Deletion in 17p	2/8 (25.0)
TP53 mutational status, Mutated, n/N (%)	2/8 (25.0)
TP53 deleted and/or mutated, n/N (%)	2/8 (25.0)
IGHV mutational status, mutated, n/N (%)	1/7 (14.3)

Eleven of the participants had completed 12 months of therapy at the time of the data cut. One of the non-completers developed a grade 4 infusion related reaction at the first obinutuzumab dose and one chose to discontinue at cycle 8.

Median follow-up was 15 months. Response rates and MRD negative rates three months after the end of treatment are summarised in Table 14; complete response was seen in 58% and partial response in 42%. All participants experienced at least one adverse event (Table 14). Grade 3-4 AEs were experienced in 83.3%; these included neutropenia (58.3%), febrile neutropenia (25.0%), TLS (16.7%) and infusion-related reactions (8.3%). The authors concluded that VenG could be safely administered to patients with comorbidities and at risk of TLS due to renal impairment.

Table 14 Available efficacy and key adverse event data CLL14 run-in

Outcome at EOT, %	**VenG (n=12)**
ORR	100
CR	58
PR	42
PD	0
MRD negative (peripheral blood)	91.7
MRD negative (bone marrow)	5/7 (71.4)
Adverse events, %	
Any AE	100
At least one grade 3/4 AE	83.3
Death	0

AE: Adverse event; CR: Complete response; EOT: End of treatment (3 months after completion of last cycle); MRD: Minimal Residual Disease; ORR: Overall response rate; PD: Progressive disease; PR: Partial Response.

The CS included a non-RCT of VenG by Flinn 2019[9] in the initial clinical SLR but it was subsequently excluded because it was considered not relevant to the decision problem (CS Appendix Table 7). This phase 1b single-arm study of VenG included two cohorts, those who were treatment naïve and those with relapsed/refractory CLL. Results for a subgroup of treatment naïve participants with del(17p)/TP53 mutation were also reported (n=5). The cohort with no prior treatment (and the subgroup with del(17p)/TP53 mutation) meet the wider NICE scope, but the ERG agrees the population does not meet the company's decision problem as the participants were not considered unfit. However, the ERG has summarised the limited results for efficacy and safety for context.

The study was a dose finding and safety expansion study. As part of the dose finding phase participants either received venetoclax first or obinutuzumab first during cycle 1 to reduce TLS risk. Thirty-two CLL participants with no previous treatment were administered VenG for 6 cycles and then venetoclax was given as a monotherapy until disease progression, unacceptable toxicity or completion of 1-year treatment. Twelve participants were enrolled during the dose finding phase and 20 during the safety expansion, but all received venetoclax 400mg. The study was performed in 11 centres including at least one from the UK. The key baseline characteristics of the treatment naïve cohort are summarised in Table 15.

Table 15 Baseline characteristics of participants with no previous treatment for CLL from Flinn 2019[9]

% unless stated	**N=32**
Median (range)	63 (47-73)
Male sex	63
Estimated CrCl <70 ml/min	29
ECOG PS 0 1	 50 50
TP53 mutation	16[a]
Del(17p)/TP53 mutation	16[a]
IGHV unmutated	50[a]

[a]Calculated by ERG using the total sample N as the denominator. The publication reports the proportion using the denominator as N minus missing data.

CrCl: Creatinine clearance; ECOG: Eastern Cooperative Oncology Group; PS: Performance status

Median follow-up for the treatment naïve cohort was 26.7 months (range, 16-39 months). Key results of efficacy and adverse events can be seen in Table 16. Results for 24-month PFS were in the same region as the VenG population in CLL14 but ORR and CR/CRi rates were better in this cohort. Undetectable MRD was an exploratory outcome. Rates of undetectable MRD in peripheral blood were 91% at least 3 months after the last obinutuzumab dose and 72% after median 4.4 months from the last venetoclax dose. The 'best response' rate of undetectable MRD in bone marrow was 78%. However, from patient level data it was apparent that of the 25 (78%) patients who achieved bone marrow negativity at least once, 15 of these (60%) later had either a positive blood or bone marrow test, suggesting the negativity was not sustained in the majority of patients.

Adverse event rates were similar between this cohort and the VenG arm of the CLL14 trial.

Table 16 Available efficacy and key adverse event data from Flinn 2019[9]

Outcome at EOT, %	**N=32**
PFS at 24 months	90.6 (95% CI 80.5-100%)
ORR (best response)	100 (95% CI 89-100)
CR/CRi	78 (95% CI 60-91)
PR	22
PD	12.5
MRD negative (peripheral blood) >3 months after last obinutuzumab treatment Median 12 months from last obinutuzumab treatment Median 4.4 months from last venetoclax treatment	 91 78 72
MRD negative (bone marrow) Best response achieved	 78
Adverse events, %	
Any AE	100
At least one grade 3/4 AE	78
Any SAE	34
Venetoclax discontinuation due to AE	3
Death	0

AE: Adverse event; CR/CRi: Complete response / Complete response with incomplete bone marrow recovery; MRD: Minimal Residual Disease; ORR: Overall Response Rate; PD: Progressive Disease; PFS: Progression-free Survival; PR: Partial Response; SAE: Serious Adverse event

Some efficacy data for the del(17p)/TP53 mutated subgroup were also reported and are summarised in Table 17, although the ERG note the small sample size rendering comparison unreliable.

Table 17 Efficacy data for the del (17p) / TP53 mutation subgroup from Flinn 2019[9]

Outcome at EOT, %	**N=5**
ORR (best response)	100
CR/Cri	60
PR	40

CR/CRi: Complete response / Complete response with incomplete bone marrow recovery; ORR: Overall Response Rate; PR: Partial Response

4.8.2 GClb studies

CLL11 trial

The company refers widely to the CLL11 trial (Goede 2014[31]) for external validation of the GClb arm. CLL11 was the pivotal trial in TA343 of Obinutuzumab in combination with chlorambucil for untreated CLL.[32]

The 3-arm trial compared chlorambucil, GClb and rituximab with chlorambucil in people with previously untreated CLL and comorbidities reflected in either ≥6 on CIRS or CrCl 30-69

ml/min, therefore the target population is similar between the two trials. However, while the CS states that CLL14 does not include patients who would receive FCR or BR in clinical practice (CS Table 2), CLL11 included people unsuitable for fludarabine-based treatment; some of these were suitable for bendamustine treatment. NICE recommends GClb only for the subgroup for whom bendamustine-based therapy is not suitable.[32] This subgroup is more relevant to the CLL14 trial, however results have not been not published.

Key baseline characteristics such as age, sex, Binet stage, CIRS >6, IGHV mutation status and del(17p) status were similar (difference <10%) between GClb arms in the CLL11 and CLL14 studies (although TP53 mutation status was not reported by CLL11). There were higher rates of cardiac and respiratory comorbidities in the CLL11 GClb arms compared with CLL14 at baseline.

The planned dose of GClb was similar between CLL11 and CLL14, except that chlorambucil was given for six cycles in CLL11 compared with twelve cycles in CLL14. The ERG for TA343 noted that the dose of chlorambucil used in CLL11 (about 70 mg) was lower than that generally used in clinical practice in England (about 120 mg).[32] The median dose intensity for chlorambucil in the GClb arm of CLL14 is reported to be 95.4% (range: 4%–111%), but it is not clear how this relates to clinical practice.

Overall, the CLL14 and CLL11 trials are similar in most aspects, although there are some key differences.

ERIC study

A recent retrospective multi-centre study (ERIC[26]) assessing the use of obinutuzumab with or without chlorambucil in 437 treatment-naïve patients from Europe, Israel, Canada and Argentina in a 'real-world' setting was identified by the ERG. The majority of patients received GClb (n=408). Those with del(17p) or TP53 mutations were excluded from the study.

The target population is similar between CLL14 and ERIC, in that the participants are described as 'unfit'. However, there are a few differences in baseline characteristics between CLL14 and the GClb cohort of ERIC. Although the median age in ERIC is similar to CLL14, the minimum and maximum ages are higher suggesting a slightly older participant group, and median time from diagnosis for the whole cohort in ERIC is longer (although it is unclear if this is measured to the

same point in the treatment history). There are also slightly fewer men in ERIC. The CLL14 trial required participants to have a total CIRS score > 6 or CrCL <70 ml/min. In ERIC, the proportion with CIRS >6 is lower than in CLL14, but the proportion with CrCL <70 ml/min is higher. Binet stages are generally similar in both studies. The ERIC study doesn't report the presence of cardiac or respiratory comorbidities and overall it is unclear whether the ERIC population is less or more fit than the population of CLL14.

Treatment with GClb was for 6 cycles in ERIC, in line with the regimen used in the CLL11 study (see Section 4.8.2). This is different to CLL14 where 12 cycles were used. The study periods in the two studies are similar: ERIC included patients who were treated during 2014-2019, while CLL14 recruited patients 2015-2016, but median follow-up was shorter in ERIC (14.1 months) than CLL14 (39.6 months).

4.9 Conclusions of the clinical effectiveness section

The evidence for the effectiveness of VenG compared with GClb for people with untreated CLL with coexisting conditions which make FCR/BR based therapy unsuitable, is from a good quality RCT. Improved PFS, CR and DOR were found with VenG, but no difference in OS was observed. Despite the submission of a more recent data-cut by the company, data remain immature for some key outcomes. The ERG noted concerns regarding the generalisability of the CLL14 trial to the UK population.

There is no head-to-head comparison between VenG and ibrutinib for the subgroup with del(17p)/TP53 mutation. Naïve indirect comparisons with three ibrutinib studies produced hazard ratios that suggested that VenG was inferior to ibrutinib for PFS and OS, however the concerns around the suitability of the comparison and the width of the confidence intervals mean that no conclusion of superiority can be drawn. The company used two different methods in the CS to identify the subgroup with del(17p)/TP53 mutation, resulting in different sample sizes between the clinical and cost-effectiveness sections. The rationale for using different algorithms is not adequately justified by the company, although it has little impact on the results.

5 COST-EFFECTIVENESS

This chapter reviews and appraises the submitted evidence on the cost-effectiveness of VenG for untreated CLL. Section 5.1 gives the ERG's critique of the company's systematic reviews. Section 5.2 provides a summary and critique of economic aspects of the CS. Section 5.3 presents the ERG's preferred base case estimates and additional work carried out by the ERG. Section 5.4 provides the conclusions of the cost-effectiveness section and section 5.5 looks at the impact on the incremental cost-effectiveness ratio (ICER) of additional analyses.

The CS was received on 29 October 2019. This submission was based on CLL14 trial data available from the August 2018 data cut (28.1 months median follow-up time from randomisation) and is referred to as the original CS. In addition, as explained in Section 4.4.1, the company submitted additional information to the ERG as follows:

- Responses to ERG's request for clarifications on the original CS. This is referred to as the 'original CS clarification responses'.
- Updated analysis, submitted as an addendum, taking into account a newer data cut-off (August 2019, 39.6 months median follow-up time from randomisation). This is referred to as the 'CS addendum'.
- Responses to ERG's request for clarifications on the CS addendum. This is referred to as the 'CS addendum clarification responses'.

Similarly, the original economic model was received on 29 October 2019 and it was based on the CLL14 August 2018 data-cut. Additional models were submitted subsequently, in response to clarification queries and availability of newer data (see Section 5.2 below).

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost-effectiveness review

The company carried out and reported a SLR of cost-effectiveness evidence. The aim of the review was to identify studies within the literature on previously untreated CLL that reported (i) relevant economic evaluations, (ii) health-related quality of life (HRQoL), and (iii) costs and use of health care resources. The scope of the search is broader than final NICE scope as it is not restricted to any specified treatment or subpopulation. Literature searches were initially carried out in December 2018 and were subsequently updated in July 2019.

Searches were conducted in a range of sources, including key electronic bibliographic databases (MEDLINE, Embase, EconLit, DARE, NHS-EED, HTA and Cochrane Library Databases), conference abstract books, HTA websites, databases and reference lists of relevant published systematic and non-systematic reviews. The ERG deems these sources to be appropriate for the identification of relevant literature. Search terms were split into key 'topics' (facets) including treatment setting, condition, cost-effectiveness, health care resource use and costs and HRQoL and terms relating to each topic (including synonyms and MeSH terms) were combined using appropriate operators. A more limited search was conducted in the Cochrane Library via CENTRAL and CDSR.

Searches in bibliographic databases sought to identify literature published over an appropriately long period of time (inception to the date of search), though relevant literature on the particular treatment combinations is likely to be recent. Manual searches of abstracts from conference proceedings of major conferences covered the period from 2016 to July 2018.

5.1.2 State the eligibility criteria used in the study selection and comment on whether they were appropriate.

Identified studies were assessed against predetermined inclusions and exclusions criteria. These are given in Table 18 (reproducing CS Appendices Table 18).

Table 18: Eligibility criteria for the economic evaluations SLR (reproducing CS Appendices Table 18)

PICOS	Inclusion criteria	Exclusion criteria
Population	• Adult patients (≥18 years)* • Human • Established 1st Line CLL (CLL or B-CLL b-cell CLL or SLL) • With or without del(17p) or *TP53* mutation • ± including patients who are suitable and unsuitable for FCR/BR	• Patients without established 1st line CLL • Paediatric patients (<18 years) • Animal studies • In vitro studies • Patients with aggressive Non-Hodgkin's lymphoma (Richter's transformation or pro-lymphocytic leukaemia)
Intervention	• No restrictions applied	• N/A
Comparator	• No restrictions applied	• N/A

Outcomes	• Total costs • Quality-adjusted life years • ICERs/whether cost effective at some ICER threshold. • Cost per life year gained • Cost per progression free year	• Any outcome not specified under inclusion criteria
Study Design	• Economic Evaluations, such as • Cost utility analysis • Cost effectiveness analysis • Cost minimization analysis	• Economic evaluations not reporting outcomes of interest. • Study designs not specified under inclusion criteria
Publication Type	• Full text articles	• Review articles** • Notes • Erratum • Comments • Editorials • Letters
Language	• Publications in English^	• Publications in any language other than English

*Studies were excluded if the average age of the population is lower than 18. The inclusion of individual patients younger than 18 years of age in an otherwise adult population did not make the article ineligible for inclusion.
**Economic evaluations published in peer-reviewed journals or conference abstract proceedings will be limited to English publications. Evidence from HTA reports will not be restricted to English as it is expected to be published in national languages of the respective HTA agencies.
^Reviews and network meta-analyses will be checked for bibliographic references ONLY and will not be extracted.
Abbreviations: BR: bendamustine in combinations with rituximab; B-CLL: B-Cell Chronic Lymphocytic Leukemia; CLL: Chronic Lymphocytic Leukemia; FCR: Fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio. **Source:** AbbVie Data on File (Previously untreated CLL economic SLR report) [10]

As anticipated, certain selection criteria (such as those related to population, comparators, publication type and language) were shared between the clinical effectiveness and cost-effectiveness SLRs. No particular concerns are raised by the ERG in relation to these criteria, though of note is the restriction to studies focusing on adults aged ≥18 years and the exclusion of studies published in languages other than English. The former restriction is in line with the population of participants in CLL14 but is narrower than the NICE scope (which does not specify an age limit), while the latter is a common practice grounded on practical reasons.

Within the cost-effectiveness SLRs, separate sets of inclusion and exclusion criteria were used for selecting literature on HRQoL and health care resource use and costs. While criteria related to population, intervention, comparator and language were identical to those used in identifying relevant economic evaluations (presented in Table 18), some criteria were appropriately different and tailored to capture evidence specific to HRQoL and resource use (e.g. criteria related to outcomes, study design and publication type) (Table 19 and Table 20 below).

Table 19. Eligibility criteria for the health-related quality of life studies (partially reproducing CS Appendices, Table 28)

PICOS	Inclusion criteria	Exclusion criteria
Outcomes	• Disutility and utility measures which comply with one of the following: • Health State Utility values elicited using direct methods: time trade-off and standard gamble • Preference-Based methods: (e.g. EQ-5D, HUI3, SF-6D, aqol, QWB) • Visual analogue scale • Oncology-specific HRQOL tools (e.g.: FACT-Leu; MRC/EORTC QLQ-Leu)	• Any outcome not specified under inclusion criteria
Study Design	• Clinical trials • Observational studies	• Phase I clinical trials • Individual case reports • Systematic Reviews* • Non-systematic reviews* • Genetic/biochemical studies
Publication Type	• Full-text articles • Conference abstracts	• Review articles • Notes • Erratum • Comments • Editorials • Letters

*Reviews and network meta-analyses will be checked for bibliographic references ONLY and will not be extracted. Abbreviations: aqol: assessment of quality of life; B-CLL: b-cell chronic lymphocytic leukaemia; CLL: chronic lymphocytic leukaemia; EQ-5D: EuroQol 5-dimension; FACT-Leu: functional assessment of cancer therapy – leukaemia; HRQoL: Health related quality of life; HUI3: Health utility index 3; MRC/EORTC QLQ-Leu: Medical research council/ European organisation for research and treatment of cancer quality-of-life questionnaire; N/A: not applicable; QWB: Quality of wellbeing; SLL: small cell lymphocytic leukaemia; SF-6D: Short-form 6 dimension; Source: AbbVie Data on File (Previously untreated CLL economic SLR report)

Table 20. Eligibility criteria for the healthcare cost and resource use studies (partially reproducing CS Appendices, Table 32)

PICOS	Inclusion criteria	Exclusion criteria
Outcomes	• Outpatient and inpatient healthcare resource utilisation • Direct costs of inpatient and outpatient services • Indirect costs	• Any outcome not specified under inclusion criteria

	• Costs of adverse events	
Study Design	• Economic evaluations • Patient chart reviews • Patient and disease registry studies • Claims data analyses	• Clinical Trials (Phase I/ II/ III/ IV) • Studies not reporting outcomes of interest
Publication Type	• Full-text articles	• Review articles** • Notes • Erratum • Comments • Editorials • Letters
Language	• Publications in English	• Publications in any language other than English
**Reviews and network meta-analyses will be checked for bibliographic references ONLY and will not be extracted. Abbreviations: B-CLL: b-cell chronic lymphocytic leukaemia; BR: bendamustine and rituximab; CLL: chronic lymphocytic leukaemia; Fludarabine, cyclophosphamide and rituximab, N/A: not applicable; SLL: small cell lymphocytic leukaemia. Source: AbbVie Data on File (Previously untreated CLL economic SLR report)		

Overall, the selection criteria employed are deemed suitable and appropriate for the purposes of the undertaken reviews.

5.1.3 What studies were included in the cost effectiveness review and what were excluded?

The SLRs carried out by the company identified 43 economic evaluations, 20 studies providing information on HRQoL and 16 studies giving estimates of healthcare resource use and costs. Only a small number of these studies was used in the submitted economic analysis. In relation to identified economic evaluations, the company stated that none of the identified studies pertained to the decision problem of interest in this submission and therefore none were directly relevant for decision-making. The ERG concurs that the identified studies do not address the exact decision problem that this technology assessment is concerned with and agree that a *de novo* economic analysis was required.

Information on resource use, costs and HRQoL sourced from the available literature was used in the form of inputs in various components of the economic model, including calculations of costs and estimation of quality-adjusted life years. As anticipated, some key information, including parameter values and assumptions, were also drawn from completed NICE technology

appraisals in CLL. The suitability and appropriateness of using specific pieces of information in respective parts of the economic analysis is critiqued in Section 5.2.

5.1.4 What does the review conclude from the data available?

The SLRs presented in the CS identified a number of studies meeting the inclusion criteria, though these studies do not directly address the decision problem concerning this appraisal. The ERG agrees that a *de novo* economic evaluation tailored to the requirements of the specific final scope and decision problem was necessary. While there is no paucity of information on a number of aspects, such as costs and health state utility values (HSUVs), in the public domain (including peer-reviewed publications and previous NICE technology appraisals (TAs)), much of this information has not been produced with the specific decision problem in mind and its applicability to the submitted economic analysis needs to be judged on a case-by-case basis. Nevertheless, the ERG believes that, using existing published evidence (e.g. in peer-reviewed studies and previous NICE TAs) can serve as useful input in the submitted economic model.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

As part of their submission to NICE, the company made available a description of their economic analysis and a decision model developed and presented in Microsoft Excel®. This is referred to as the 'original CS model'. Updated models, based on the original model but featuring amendments, were also submitted alongside other evidence in the following instances:

- As part of the company's responses to the ERG's request for clarifications on the original CS. This is referred to as the 'original CS clarification responses model'.
- As part of the updated analysis, submitted as an addendum (August 2019 data cut). This is referred to as the 'CS addendum model'.
- As part of the company's responses to the ERG's request for clarifications on the CS addendum. This is referred to as the 'CS addendum clarification responses models'.

A summary and critique of the submitted economic evidence is presented below.

5.2.1 NICE reference case checklist

The NICE Reference Case checklist is given in Table 21 below.

Table 21: NICE Reference Case checklist

Element of health technology assessment	NICE Reference Case	Does the submission adhere adequately to the Reference Case?
Defining the decision problem	The scope developed by NICE	Yes (also see discussion about differences in Section 3 above)
Comparator(s)	As listed in the scope developed by NICE	Yes (also see discussion in Section 3.3 above)
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and Personal Social Services	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes. A systematic review was conducted. Key information is drawn from data collected in the CLL14 trial. Further information and model parameters have been obtained from the existing literature and available NICE Single Technology Appraisals.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Partially (the utility value used for 'progression-free, off IV treatment' was elicited through vignettes)
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

Evidence on resource use and costs	Costs should relate to NHS and Personal Social Services resources and should be valued using the prices relevant to the NHS and Personal Social Services	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Abbreviations: NHS: National Health Service; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year.		

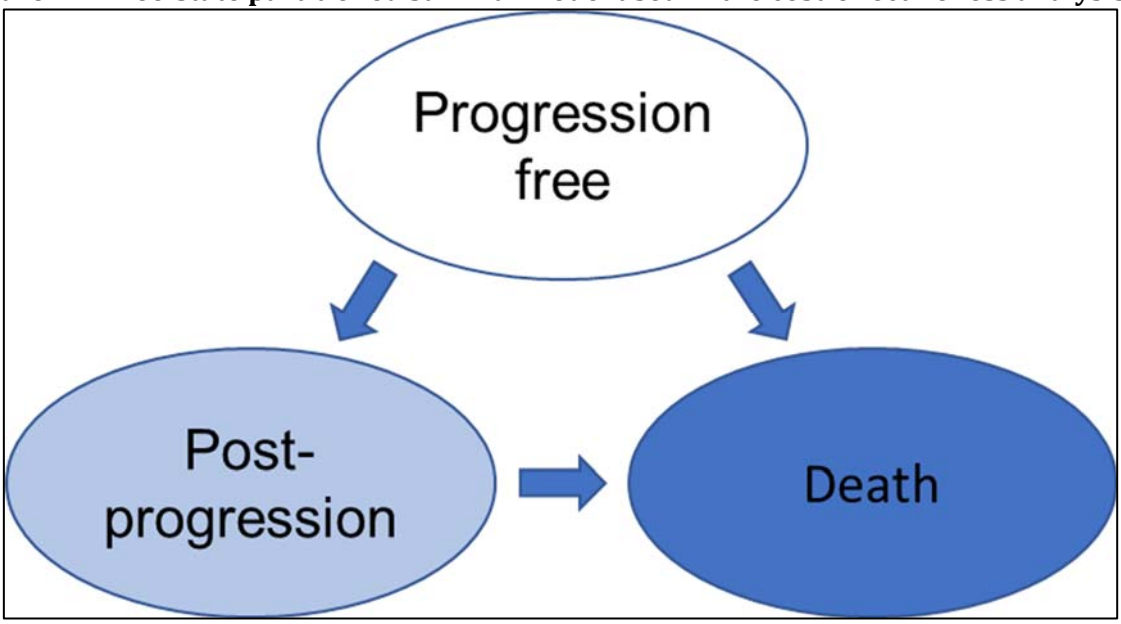
5.2.2 Model structure

The economic model submitted as part of the CS follows a partitioned survival approach and comprises three health states:

- Progression-free survival (PFS, also referred to as pre-progression state), which is populated by CLL patients who are alive and have not progressed.
- Post-progression survival (PPS, also referred to as post-progression state), which includes CLL patients who are alive but have progressive disease, and
- Death, which is the final, absorbing state populated by deceased CLL patients.

The model has a maximum time horizon of 30 years (in the base-case analysis) and is evaluated over a series of cycles, each lasting 28 days. The model's cycle length matches the dosing schedule (length of treatment cycles) for VenG and its comparators. A half-cycle correction has been used in the calculations. The company's representation of the model structure is given in Figure 1 (reproducing Figure 18 in the CS) below.

Figure 1: Three-state partitioned survival model used in the cost-effectiveness analysis



The model structure depicted above was used for both comparisons presented in the CS, namely (i) VenG vs. GClb in patients without del(17p)/TP53 mutation for whom FCR/BR treatment is unsuitable, and (ii) VenG vs ibrutinib in patients with del(17p)/TP53 mutation. Briefly, patients enter the model in the PFS state, where they receive one of the first-line treatments. Patients remain in the PFS state until they die or experience disease progression, upon which event they transition to the Death or the PPS state, respectively. Patients in the PPS state may remain in the state or die, in which case they reach the absorbing state - Death. The proportion of the modelled cohort within each of the three health states at each point in time is guided by extrapolated PFS and OS curves. Of note is the fact that initiation of subsequent treatment is informed by TTNT curves, rather than assumed to take place instantaneously upon progression to PPS. Death due to causes other than CLL (i.e. background mortality) was guided by age-adjusted and sex-adjusted mortality risk values drawn from UK life tables published by the Office for National Statistics [33].

On the whole, the ERG believes that the type and structure of the submitted model is appropriate for the purposes of the condition investigated and adequate for the decision problem considered in this appraisal. The pathway employed in the model is in line with expectations around the clinical progression of the disease, while the structure of the model is generally suitable for capturing and quantifying key costs and health outcomes associated with the compared treatments. A more complex structure (for example, a structure employing sub-states that further distinguish between patients on-treatment or off-treatment in various health

states) may have resulted in a more accurate representation of patients' experience, however the ERG considers that the submitted, parsimonious model is adequate and appropriate for this appraisal.

5.2.3 Population

As discussed in Section 3.1 above, the CS, including the submitted models, relates to a narrower population than that specified in the NICE decision problem. It focuses on VenG in two populations:

- Patients with previously untreated CLL, without del(17p)/TP53 mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR.
- Patients with previously untreated CLL, with del(17p)/TP53 mutation.

The CS populations are similar to those defined as relevant subgroups for consideration in the NICE final scope for this appraisal (See Section 3.5 above) nonetheless, in the CS they constitute the key population groups of interest. Mutation status (i.e. del(17p) and/or TP53 mutation being present) have been combined into a single sub-population, on the premise that these mutations are known to share similar prognostic information. Different algorithms were used to categorise patients to mutation status for use in the CSR and the cost-effectiveness model (CEM).

In response to ERG requests for clarity, the company stated that CLL14 trial participants were assigned to the two mutation status subgroups according to the following algorithm:

- If del(17p) is abnormal (determined by central lab), variable = 1
- If del(17p) is normal (determined by central lab), variable = 0
- If del(17p) is missing & TP53 is mutated, variable = 1
- If del(17p) is missing & TP53 is unmutated, variable = 0
- Else if both are missing = NA

While the ERG accepts that it is reasonable to combine mutation status involving del(17p)/TP53 mutation into a single variable, the ERG sought to understand the company's rationale for using different approaches for mutation status categorisation in the CSR and CEM analyses and the impact that this may have on the results. Clarifications were sought from the company in

relation to subgroup numbers in the CSR and CEM analysis presented in the original CS and the CS addendum, and the discrepancies between them (see Table 22).

In their response, in addition to alluding to errors in the CSR that have been addressed in a corrigendum, the company stated that differences in approaches to combining del(17p)/TP53 mutation status between the CSR analysis and the CEM analysis are due to the latter being derived from a programming method that was used for combining del(17p)/TP53 mutation status in the CEM analysis for NICE TA561.[34] It was further clarified that *"the CEM analysis algorithm prioritises the del (17p) status, whereas the CSR analysis algorithm considers the del(17p) status and TP53 status individually."* (CS addendum clarification response B6).

Table 22: Population numbers utilised in the CSR and CEM analyses

	CSR Analysis **(original CS, Table 32)**	CSR Analysis **(CS addendum, Table 16)**	CEM Analysis **(original CS, Table 32)**	CEM Analysis **(CS addendum, Table 16)**
Non-del(17p) / *TP53* mutation	386	368	387	391
Del(17p) / *TP53* mutation	46	49	31	31
Undefined	0	15	14	10
Total	432	432	432	432
Abbreviations: CEM: cost-effectiveness model; CSR: clinical study report.				

To evaluate the extent to which the use of a different algorithm for CEM impacts on the calculated results, the ERG asked the company to provide a new version of the economic model where cost-effectiveness results were calculated according to time-to-event (TTE) inputs accruing from the CSR (rather than the CEM) categorisation. Using the CSR categorisation in the model resulted in a small difference in the cost-effectiveness results for VenG against its comparators GClb and Ibrutinib in the non-del(17p) and the del (17p) model populations, respectively. The ERG accepted the CEM mutation status categorisation as an appropriate basis for economic modelling.

5.2.4 Interventions and comparators

The comparisons addressed in the company's economic submission and the corresponding populations are described below in Table 23 (reproducing Table 1 in the CS).

Table 23: Sub-populations considered in this submission

Population	Comparison	Rationale
Subpopulation 1: Patients with previously untreated CLL, without del(17p)/*TP53* mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR	VenG vs GClb	• This subpopulation best reflects the cohort of the pivotal trial, CLL14 • The subpopulation is consistent with NHS clinical practice; clinical experts treating patients with CLL in the UK NHS have confirmed that VenG would not be used in

		patients suitable for fludarabine- or bendamustine-based therapies
Subpopulation 2: Patients with previously untreated CLL, with del(17p)/*TP53* mutation	VenG vs ibrutinib monotherapy	• This subpopulation is also reflected in the pivotal trial, CLL14, where 10.6% of patients has del(17p)/*TP53* mutation • There is a high unmet need for this poor-prognostic subpopulation
Abbreviations: CLL: chronic lymphocytic leukaemia; GClb: chlorambucil with obinutuzumab; NHS: National Health Service; VenG: venetoclax with obinutuzumab.		

In the economic model, venetoclax is administered as an oral tablet over a fixed treatment duration of 12 cycles. The treatment is delivered with an initial dose escalation schedule (from 20mg to 400mg daily over cycles 1 and 2, followed by 400mg daily over cycles 3-12). Obinutuzumab is administered as an intravenous infusion, over a fixed treatment duration of 6 cycles, in line with the administration schedule in CLL14.

In the company's analysis, chlorambucil (Clb) is considered to be administered orally over 12 cycles, as per the treatment schedule in the control arm of CLL14. This schedule, however, is not aligned with Clb use in UK clinical practice, where the drug is typically administered over six cycles. The company acknowledged this discrepancy and argued that the overall dose, which is likely to have a larger impact on efficacy than the number of cycles, is broadly similar to the overall dose administered in UK clinical practice. According to the company, experts at an AbbVie-organised HTA advisory board opined that the difference in the number of cycles should not be a concern because 12 cycles of GClb as used in the control arm of the CLL14 trial would most likely lead to better results than six cycles, making the modelled comparison more favourable to GClb and conservative for VenG. No further evidence was offered to substantiate this opinion.

Advice sought from the ERG's clinical expert confirmed that the overall dose is likely to have a larger impact on efficacy than the number of cycles, thus the regimens are comparable in terms of efficacy. The ERG's clinical expert considered the assumption of equivalence between the six and 12-cycle Clb regiments to be reasonable and opined that most CLL experts would advocate 12 months of chlorambucil-based therapy. However, our expert confirmed that, in UK clinical practice, Clb is typically offered over six cycles. In light of this, and to identify the impact of this shorter treatment schedule, the ERG requested an additional analysis where Clb is administered over six cycles. In their response, the company pointed to variability in the UK practice in relation to Clb dose and number of cycles and provided alternative versions of the model based

on a six cycle treatment schedule and alternative doses and points of treatment delivery within each cycle (0.5mg, 0.10 mg, on days 1 and 7 or 1 and 15). It is noted that changing the number of cycles from 12 to six in the model required the doubtful assumption that the efficacy benefit of a 12-cycle Clb treatment (rather than a possibly reduced 6-cycle efficacy benefit) as per the CLL14 trial outcomes is maintained.

The change to a six-cycle schedule had a very small impact in the calculated cost-effectiveness results. In consultation with the NICE Technical Team, it was agreed that the original analysis, based on the 12-cycle treatment schedule, provides appropriate and informative findings, thus the main results are provided on the basis of the 12-cycle treatment schedule.

5.2.5 Perspective, time horizon and discounting

The analysis is presented from an NHS and Personal Social Services perspective, in line with the NICE reference case. Patients are modelled over a 30 year time horizon, which for a typical cohort of CLL patients effectively constitutes a lifetime horizon. In the base-case, costs and benefits were discounted at an annual rate of 3.5%.

5.2.6 Treatment effectiveness and extrapolation

The company use four time-to-event outcomes from CLL14 as inputs into the economic model: PFS, OS, TTNT, and time on treatment (ToT). Extrapolations were assessed through a combination of information criteria, Akaike and Bayesian information criteria (AIC and BIC), assessment of visual fit and assessment of the clinical plausibility of long-term predictions. Each extrapolation was subject to constraints in case the hazard rate of the extrapolation was too optimistic.

For each defined population (i.e. patients without del(17p)/TP53 mutation and patients with del(17p)/TP53 mutation), we present a summary of the company's implementation of each input based on their CS addendum, accompanied by the ERG's critique and recommendations.

5.2.6.1 Non-del(17p)/TP53 mutation population: progression-free survival

Proportionality

The company assessed and rejected the assumption of proportional hazards between the two arms of CLL14 for PFS. This was done through an assessment of Schoenfeld residuals and a

formal test of proportionality. The test for proportionality did not lead to a rejection of the hypothesis that proportional hazards held (p=[redacted]), though the threshold for significance was not clearly stated. However, the Schoenfeld residual plot had a clear curvilinear trend suggesting that the proportionality assumption did not hold. An examination of the log-cumulative hazard plot showed that the curves crossed at roughly 6.5 months and then gradually diverge also suggesting that the hazard rates were not proportional. Whilst the population that proportionality was evaluated on included both patients with and without del(17p)/TP53 mutation, the ERG have no reason to believe that the proportionality assumption between treatments would be different for these two groups, and agree that proportionality across the follow-up period does not hold.

Despite the likely violation of proportional hazards, using dependent models does have other advantages. Given the immaturity of the data, it can be beneficial to use data from both arms to ensure hazard rate behaviour is consistent and plausible for both arms. The company utilised this approach in the appraisal for venetoclax-rituximab for second-line CLL,[34] where they assumed proportionality between PFS and OS and between both treatments simultaneously. By making these assumptions, one can reduce the uncertainty around each extrapolation, through the borrowing of information.

Constraints

The PFS extrapolations were subject to the following constraints:

- there could not be more patients in the progression-free health state than there were alive.
- the hazard rate of disease progression could not fall below the hazard rate of background mortality.

The ERG accepts the rationale behind the first constraint, which is routinely implemented in partitioned survival models such as this. However, the reasoning for the second constraint is less clear. The ERG believes that it may not be true that the PFS event rate should always be higher than background mortality. The ERG accepts that the overall mortality rate of the CLL14 trial should never drop below that of background mortality. However, it is the healthiest patients who will remain in the progression-free health-state population, and the ERG finds it plausible that they may have a progression/mortality rate below that of background mortality. This constraint applied by the company may unnecessarily increase the PFS event rate, potentially introducing bias into the cost-effectiveness analysis.

Extrapolations

The company compared standard parametric extrapolations fitted separately to each arm of the PFS data: exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz curves. The effect of the del(17p)/TP53 mutation was modelled through the inclusion of a covariate in the parametric model. This assumed proportionality of either the hazard rate or the failure time, depending on the parametric curve being fitted. This meant that the effect of the del(17p)/TP53 mutation was modelled separately for both arms. This is of concern to the ERG, as it reduces the information contributing to each effect estimate suggesting each will be surrounded by large uncertainty, though this uncertainty was not made clear by the company. There is also no evidence either in support or against the assumption of an interactive effect between the deletion/mutation and treatment.

Figure 2, taken from the CS, demonstrates that there are clear differences between the PFS extrapolations for both arms, but particularly among the VenG extrapolations. Note that the extrapolations in this figure have not been subject to the constraints mentioned above.

Figure 2: PFS extrapolations from CLL14 for patients without del(17p)/TP53 mutation, unconstrained

The company presents the AIC and BIC statistics for the parametric curves, shown here in Table 24, and long-term predictions for the extrapolations (Table 25), which have had the constraints applied, explaining the inconsistency with Figure 2.

The constraints implemented by the company come into effect in both arms of the trial. For VenG, the background mortality rate is used instead of the PFS extrapolation from 10.9 years in the economic model, and for GClb from 16.9 years.

Table 24: AIC and BIC for PFS models fitted independently to arms of CLL14 trial

Distribution	AIC		BIC	
	VenG	GClb	VenG	GClb
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Table 25: PFS predictions from parametric models fitted to CLL14 trial and benchmarks

Distribution	VenG				GClb			
	3 year	5 year	10 year	20 year	3 year	5 year	10 year	20 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLL11 (95% CI)	-	-	-	-	42%	25% (19-31)	-	-
ERIC study	-	-	-	-	42%	-	-	-
CLL14	81.9%	-	-	-	49.5%	-	-	-
ERG Clinical Expert	75%	50%	20%	5%	40%	25%	0%	0%
2 knot hazard spline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Both AIC and BIC suggest that the exponential curve is the best fit to the VenG data, but that the log-logistic curve is the best fit to the GClb arm.

The company states that their statistical experts advised that statistical fit should not be relied upon when data are immature. The ERG agrees and are reluctant to allow AIC and BIC to influence the choice of curve given the immaturity of the data.

The company rejects the exponential curve as selecting this for both arms would result in an assumption of proportional hazards which has already been concluded as false. The ERG also agrees with this consideration, also noting the exponential extrapolation for GClb is too optimistic.

The company then compares the extrapolation to the observed data from CLL11[35], since both trials had a GClb treatment arm. The log-logistic and the Weibull models provide the closest predictions to the observed 5 year PFS from CLL11, however slightly overestimate and underestimate respectively. The company reports selecting the log-logistic for their base case analysis through consideration of the goodness of fit combined with an examination of the plotted hazard functions. However, the company does not elaborate on exactly how the hazard functions influenced their decision making process. The company concludes by reporting that clinical experts validated the log-logistic curve as the closest to clinical practice for GClb patients.

The ERG note that the independent extrapolations considered by the company all overestimate the three year PFS rate in both arms, and considerably overestimate the three year PFS rates for the comparable GClb groups from CLL11 and the ERIC study[26] (see section 4.8), and the predictions of the ERG's clinical expert.

The ERG has some concerns with the company's justification in selecting the log-logistic curve. Firstly, the data immaturity means extrapolation with any curve is unlikely to accurately capture the true survival profile for patients in either arm.

Secondly, when the ERG considers the hazard function of the log-logistic curve, without constraints applied, the nature of the log-logistic curve is to model a decreasing hazard rate beyond the tail of the Kaplan-Meier (KM) plot for both arms. The ERG finds this implausible, given that OS events for progression-free patients are included in this measure. This view appears to be supported by the company in their original submission. When assessing the proportionality assumption for TTNT using the previous data cut, the company states that they

expected the assumption to be rejected due to the "close correlation" between PFS and TTNT. They later reject the log-logistic as a candidate model for TTNT due to the decreasing hazards over time since it is "clinically implausible". It is unclear why the company was willing to select the log-logistic curve for PFS but not for TTNT, despite the correlation between the outcomes.

The fact that the hazard rates for the extrapolations of both arms fall below background mortality reinforce the ERG's view that the extrapolations are unsuitable.

The ERG also compared the mean PFS time from the company's base case analysis, and contrasted it to that from the appraisal of GClb for the same indication (TA343). Both the company's and the ERG's base case from the initial review of TA343 estimated the undiscounted mean time in the PFS health state to be 2.83 life years (LYs). In the present appraisal, the log-logistic extrapolation preferred by the company estimates this mean time for PFS to be [redacted] LYs.

The ERG is reluctant to recommend any of the independent PFS extrapolations presented by the company based on the immaturity of the data and the implausibility of the extrapolations, and so we considered alternative extrapolations.

The alternative approaches made available by the company in the economic model included the option to use spline models to extrapolate PFS or to model using KM data followed by a parametric extrapolation in a piecewise approach, however these were not discussed in the CS.

For completeness, the ERG investigated the plausibility of the extrapolations for 60 PFS models, consisting of the combinations of dependent and independent, parametric and spline models, fitted with and without the KM data. The extrapolations that were used after an initial period of KM data were still fitted to the full observed set of data, and not only to the tail data. The ERG found that these models apply the predicted hazard rate to the observed data from 28 months, and were just a small step change from the extrapolations that are performed without prior modelling of the KM data. It is unclear why the company selected the cut-off of 28 months, however this setting could be varied within the economic model.

The ERG found that the spline model with 2 knots fitted on the hazard scale predicted a 5 year PFS rate of [redacted]% for GClb, the closest of all independent models to the observed data from CLL11. The corresponding estimate for mean PFS was [redacted] LYs, an improvement over the

company's base case, closer resembling estimates from the extrapolations of TA343. The 10 year estimate for VenG PFS was also consistent with the prediction of the ERG's clinical expert.

These extrapolations for PFS could still be overoptimistic in terms of their estimates of proportion estimated to be progression-free and mean PFS time for both arms, but are the most plausible from the data in its current state of maturity.

5.2.6.2 Non-del(17p)/TP53 mutation population: Time-to-next treatment

Time-to-next treatment is used in combination with OS to estimate a pseudo-health-state that the ERG will refer to as "time on next treatment" (TONT). This is similar to the commonly utilised health-state in partitioned survival models of post-progression survival, in that its population size is calculated as the difference between the TTNT curve and the OS curve. However, TONT is only used to calculate the number of patients on second line treatment, and the associated costs of this treatment. There is no utility value attached to this group of patients, as this is dictated by their progression status. The TTNT is a very influential parameter in this appraisal, due to the high costs of later line therapies. As with PFS, the immaturity of the data raises concerns over the accuracy and reliability of any extrapolation.

The TTNT proportionality assessment and extrapolation were performed in a similar manner to PFS. The company rejected the proportionality assumption from examination of the observed cumulative hazard plots and residual plots. The ERG agrees with this interpretation of the evidence, though note there is a stronger argument for proportionality for TTNT than PFS, and maintain the view that the assumption may be helpful when extrapolating given the immaturity of the data. Recall that the company treated death events as TTNT events, which may confound the extrapolations.

The company considered both parametric and spline models fitted independently to both arms of CLL14.

<u>Constraints</u>

TTNT extrapolations were constrained by the following rules:

- The number of patients who had not begun their next treatment could not exceed the number of patients alive.

- The hazard rate of beginning next treatment could not fall below the hazard rate of background mortality.

Extrapolations

The company examined the AIC and BIC for all models. The exponential model was the best fit for the VenG arm. For GClb, the log-logistic is the best fit when considering both AIC and BIC. As before, the immaturity of the data leaves the ERG unwilling to rely heavily, if at all on AIC and BIC for the selection of a curve for extrapolation.

The company then compares the extrapolations to the CLL11 trial, which reported at 5 years that 49% of GClb patients had not experienced a TTNT event. In their first submission, the company rules out the log-logistic curve due to its "clinically implausible" decreasing hazard rate over time, and selected from the generalised gamma, Weibull and spline models the model with the best statistical goodness-of-fit, leaving them with the Weibull. However, in their addendum using the extended follow-up, the company prefers the log-logistic model, contradicting their earlier justification.

The company now states in the CS Addendum that the log-logistic curve aligns with the clinical expectation for patients in remission, however the ERG remains unconvinced of this justification.

The ERG is not supportive of the use of the log-logistic curve or any of the independent extrapolations for TTNT considered by the company, as no curve provides 5 year estimates which are comparable to what was observed in CLL11 (see Table 26).

Firstly, the data are immature meaning the estimated parameter values will be associated with large uncertainty and the fitted models are unlikely to capture the true behaviour of TTNT. Secondly, the constraint of the hazard rate for TTNT to not fall below background mortality is necessary and comes into effect at just before 6 years for the VenG log-logistic extrapolation and just before 14 years for the GClb log-logistic extrapolation. This implies the rate of patients beginning a second treatment or dying before beginning a second treatment is equivalent to the rate of background mortality, casting further doubt on the reliability of the extrapolations.

In search of an alternative, the ERG investigated 60 dependent and independent models with and without using KM data before the extrapolations to obtain more plausible estimates. Only two models produced estimates of 5 year TTNT that were within ± 5% of the 49% observed in CLL11. Both of these models were independently fitted probit spline models with 2 knots. Whilst the ERG interprets the resulting estimates for GClb to be plausible for these two probit spline models, the predictions for VenG were still constrained by background mortality within the first 7 years of the economic model.

The ERG also requested that the company implement extrapolations of TTNT where OS events were instead censored rather than counting as events. However, these extrapolations were no more plausible than the original ones provided by the company.

The ERG considered an alternative approach, and recreated the patient level data of CLL14 data for TTNT and PFS provided by the company within the economic model using the ipdfc command in Stata 16.[36] The ERG hypothesized that due to the similarities between TTNT and PFS, that the assumption of proportionality might hold between these outcomes, and fitted a stratified Cox proportional hazard model, stratifying by arm of the trial. A check of the cumulative hazard plots suggested that the assumption did hold (Figure 3). This produced a hazard ratio of [redacted] that the ERG applied to the hazard rates from the ERG preferred PFS curve in the economic model. The resulting 5 year prediction was within the 95% confidence interval of the estimate from CLL11, and the constraint to background mortality only came into effect beyond 20 years for both arms, where its influence was much smaller. Hence, the ERG prefers to use this approach to extrapolate TTNT over the parametric models provided by the company.

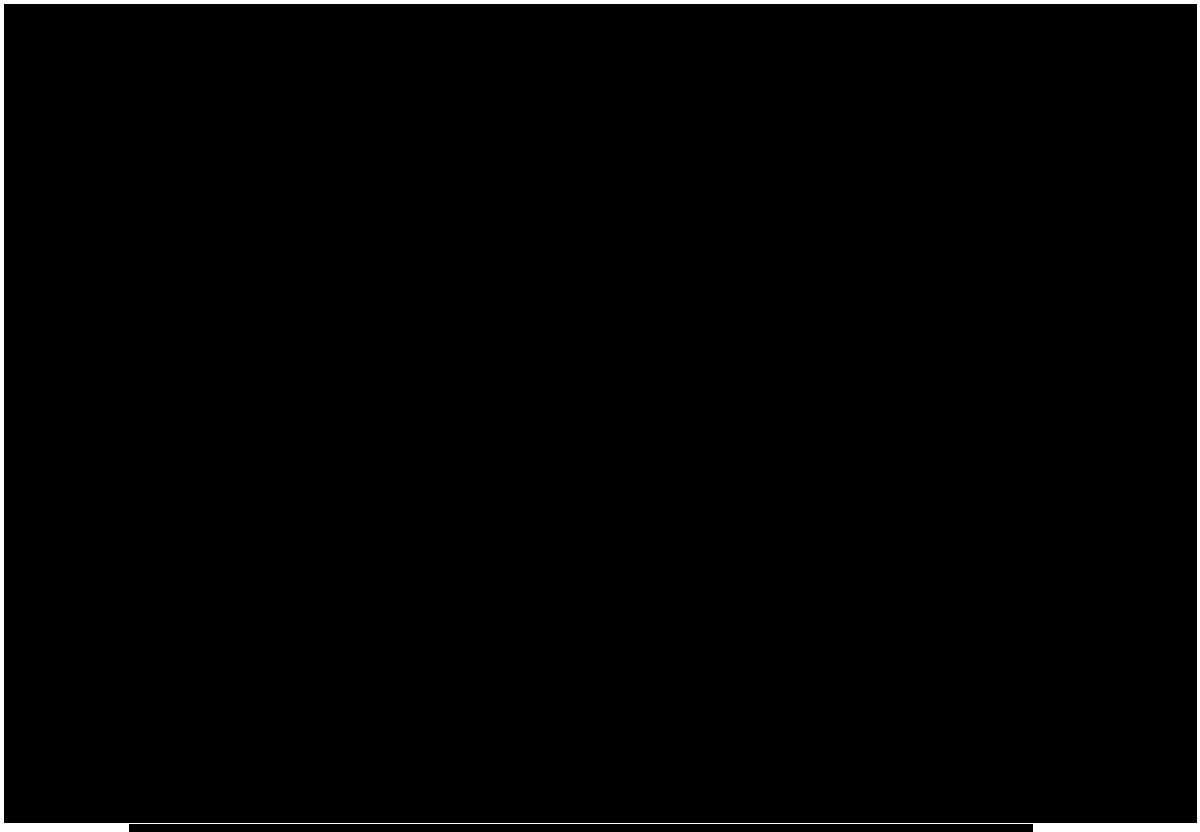


Figure 3:

Table 26: Predictions of TTNT from CLL14 data for non-del(17p)/TP 53 mutation population

Distribution	VenG			GClb		
	5 year	10 year	20 year	5 year	10 year	20 year
Exponential						
Weibull						
Gompertz						
Log-logistic						
Log-normal						
Generalised gamma						
CLL11 Data	-	-	-		-	-
ERG hazard ratio on PFS extrapolation						

5.2.6.3 Non-del(17p)/TP53 mutation population: overall survival

The company performed model selection and extrapolation for OS in an identical way to PFS and TTNT. The only constraint applied was that the hazard rate of OS could not fall below the rate of background mortality. Due to the immaturity of the data, the company assumes that the

OS for the VenG arm is equivalent to that of the GClb arm, despite including a covariate for the effect of VenG in the model. This assumption of equivalent for OS also seemingly disregards the strong benefit of VenG that was observed and modelled for PFS and TTNT. Examination of the limited follow-up suggested the data were consistent with both the assumptions of proportionality and equivalence, but it is unclear whether these assumptions are truly appropriate for either the observed period or the extrapolated period, given the immaturity of the data.

The company details their model selection, considering AIC, BIC and the hazard behaviour of the various contender models. However, this is largely irrelevant as can be seen when comparing the long-term predictions from the models in Table 27. Most of the models appear to produce very similar extrapolations, despite immature data usually being associated with large uncertainty. This similarity is due to the effect of the background mortality constraint, and not because the parametric curves necessarily agree. For the exponential model chosen by the company in their base-case, the background mortality rate comes into effect from 4.87 years. All of the models have background mortality coming into effect at a similar time, suggesting none of the extrapolations would be considered plausible without this constraint.

The company fitted models either independently to both arms, or simultaneously to both arms with a covariate for treatment effect. For their base-case, the company used an exponential model and fitted a dependent model, with a parameter for first line treatment. They then used the predicted curve for the GClb arm to represent OS for both arms.

The ERG is unclear why the company did not refit the model removing the parameter, adjusting for the arm of the CLL14, when assuming equivalence.

In their original submission, the company cites other studies with longer-term follow-up. The study with the highest absolute survival of 53% at 10 years was Shvidel et al[37] however, this study included patients who were eligible for FCR and who are likely to be a healthier population, though this effect could be negated by developments in later lines of therapy that would affect patients in CLL14.

The ERG's clinical advisor provided comment on the fact that the company's modelling of OS suggested that the OS from CLL14 was almost identical to that of the general population

meaning there is no additional risk of death from CLL, and stated this to be "untrue". The ERG also compared the company's predicted OS to the OS observed in the 5-year follow-up of CLL11. Whilst there likely are differences between the studies in terms of the later lines of therapy available, the ERG is unconvinced that this can explain the considerable difference between the company's predictions and the data observed in CLL11.

Hence the ERG is reluctant to select any of the curves considered by the company as they all provide implausible extrapolations and rely heavily on the constraint of background mortality.

Table 27: Overall Survival predictions from dependent parametric models for non-del(17p)/TP 53 mutation population

Distribution	GClb (also used for VenG)			
	3 year	5 year	10 year	20 year
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Background mortality	[redacted]	[redacted]	[redacted]	[redacted]
CLL11 GClb	[redacted]	[redacted]	[redacted]	[redacted]
ERIC Study GClb	[redacted]	[redacted]	[redacted]	[redacted]
ERG Clinical Expert		[redacted]	[redacted]	[redacted]
ERG OS using ERIC hazard rate from 3 years	[redacted]	[redacted]	[redacted]	[redacted]

In pursuit of a plausible extrapolation, the ERG considered the 60 curves incorporated by the company into the economic model, as performed for the previous time-to-event outcomes. However, none predicted 5-year survival of below 80%, and were therefore not considered consistent with the CLL11 data by the ERG.

Next, the ERG digitised KM plots and recreated patient level OS data from the CLL11 trial, and obtained patient level data from the investigators of the ERIC study. Exponential models were fitted to the data from both trials to investigate their hazard rates, however these models were

then inconsistent with the observed data from CLL14. In order to obtain a model that was consistent with both CLL14 and the external studies, the ERG considered using piecewise modelling, where the hazard rate from CLL14 was modelled for the first three years of the economic model, followed by the hazard rate from the ERIC study. The ERIC study was preferred over CLL11 since the data are more recent, and the later lines of therapy likely to be more consistent with what would be received by patients in the UK moving forward. However, the hazard rates were similar from both studies. The ERG's clinical expert also stated that the OS data from the ERIC study is "very believable and representative" of patients under this indication, given that it is real world data.

The ERG maintained the assumption of equal OS between the two arms, because although it is plausible that VenG could offer some benefit, there is no clinical evidence to support this or provide any quantification of this benefit. The ERG's clinical expert also commented that there is no evidence yet on how effective salvage therapies are after first line VenG, whereas ibrutinib is demonstrated to be effective following GClb, so it is unclear whether this assumption could be considered conservative. Under the ERG's preferred OS assumption, the constraint of background mortality comes into effect at 14 years.

5.2.6.4 Non-del(17p)/TP53 mutation population: Time on treatment

The time spent on first-line treatment outcome was not extrapolated, as the trial follow-up exceeded two years and all patients had discontinued first-line treatment within the observed period. The company modelled the observed data, however it was subject to the constraint that the proportion of patients stopping their first treatment could not exceed the proportion that had begun their second treatment, according to the modelling of TTNT. The company also adjusted ToT without providing clear justification. Instead of using the data as observed from CLL14, they restricted ToT such that no patients in the economic model could exceed the licensed duration of 12 cycles. However, following consultation with our clinical expert, the ERG concludes that it is likely these patients still appearing on treatment had experienced a pause of treatment, and to extend the time on first line treatment would effectively double count treatment costs for these patients. Hence, the ERG is satisfied with the company's modelling of time on treatment.

5.2.6.5 Del(17p)/TP53 mutation population: VenG

For the time-to-event extrapolations, the company estimated the efficacy of VenG in the del(17p)/TP53 mutation population by including the relevant covariate into the model for the

non-del(17p)/TP53 mutation population as discussed above. The rationale for doing this is that the size of this subgroup in CLL14 was too small to extrapolate from and this approach allowed the company to borrow information from the wider trial population. The company appeared to include patients who received GClb in their analysis, despite these patients being irrelevant and potentially misleading for the eventual comparison to ibrutinib. This approach makes the assumption of proportionality between the two subgroups of patients, difficult in addition to other assumptions of proportionality or equivalence made between treatment arms.

For PFS and TTNT the company used the models in the same manner as in the above sections. For OS, the company fitted the same dependent model, but this time included the covariate for the differing effect of VenG relative to GClb when predicting OS for VenG patients, in addition to including the deletion covariate. Hence, the OS for VenG patients with del(17p)/TP53 mutation was not assumed to be equivalent to the same subgroup receiving GClb. Recall, that for the population without del(17p)/TP53 mutation, the company assumed that OS for VenG patients would be equal to that of GClb patients, despite including a treatment effect parameter for VenG in their model. The rationale for the inconsistency in this assumption is unclear as it is not discussed by the company.

In response to the ERG's clarification request following the company's addendum, the company assessed proportionality between the subgroups using plots of the Schoenfeld residuals, ignoring potential treatment effects. There was no clear evidence of violation of proportionality for PFS or OS, though the small sample size of the del(17p)/TP53 mutation group makes it difficult for the ERG to be confident that proportionality is a reasonable assumption to make. For TTNT, the company only assessed proportionality for the previous data cut (August 2018), however it appeared to support the assumption of proportional hazards.

The company compared the visual fit of the extrapolations to the KM curves for VenG patients from CLL14. The ERG interpreted these and concluded that the fit to all three outcomes could be considered reasonable (Figure 4, Figure 5 and Figure 6).

In their response to the ERG clarification questions referring to the original submission, the company provided detailed model output for PFS and OS which suggested that the hazard rates of these outcomes for the del(17p)/TP53 mutation subgroup were significantly different to the hazard rates for the rest of the CLL14 population.

Figure 4: PFS from CLL14 for del(17p)/TP53 mutation population - company base case

Figure 5: TTNT from CLL14 for del(17p)/TP53 mutation population - company base case

Figure 6: OS from CLL14 for del(17p)/TP53 mutation population - company base case

5.2.6.6 Del(17p)/TP53 mutation population: ibrutinib

Given the lack of a direct comparison between ibrutinib and VenG in the del(17p)/TP53 mutation population, the company applied the hazard ratios estimated from their naïve indirect comparisons onto the extrapolations for VenG. A comparison of the log-cumulative hazard plots comparing data from Mato et al[38] suggested that the proportional hazards assumption for PFS and OS was violated, though this could be influenced by the small sample sizes. If violated, this would leave all comparisons presented by the company to be unreliable as they all assume proportionality between ibrutinib and VenG for PFS and OS.

As before PFS and OS hazard rates were constrained by background mortality, and there could not be more patients in the progression free health state than alive. The constraint with background mortality was not necessary as extrapolated mortality rates remained above background mortality for the duration of the economic model.

Time on treatment for ibrutinib was modelled to be equivalent to PFS, which is consistent with how ibrutinib is currently administered.

TTNT is not explicitly modelled for ibrutinib. This means the way the company modelled the time on next treatment for ibrutinib was inconsistent compared to VenG and GClb. For ibrutinib, the company counted only new incidences of either progressive disease events or death events within each cycle as contributors to the time-on-next-treatment. This means that across the time horizon of the model, each patient received later line therapy for a single cycle. The rationale for not considering the possibility of remaining longer on next treatment is not provided by the company, and remains unclear to the ERG.

The company's analysis was also found to have further flaws, which became apparent when investigating the Markov trace plots, which track the health-state of the population through the time horizon of the economic model.

In Figure 7 showing the Markov trace for VenG, it is apparent that there is [redacted]. Similarly, for ibrutinib, Figure 8, patients spend [redacted]. It is possible that the lack of a post-progression health state is what led the company to their unusual approach for modelling time-on-next-treatment for ibrutinib patients. The ERG is concerned with the implausibility of these outcomes from the company's analysis.

Figure 7: Markov trace for VenG in del(17p)/TP53 mutation population

Figure 8: Markov trace for ibrutinib in del(17p)/TP53 mutation population

The ERG attempted to investigate whether either of the PFS and OS extrapolation could be considered more reliable than the other, as both contribute to the construction of the post-progression health state (Table 28). A comparison of the company's predictions to the ERG's clinical advisor suggests that both the PFS and OS extrapolations may be too optimistic, and the ERG considered alternative curves.

Table 28: Comparison of PFS and OS estimates between company's and ERG's base case time-to-event outcomes for 17p deletion/TP53 mutation population.

PFS					
	Company			**ERG**	
	VenG (independent log-logistic extrapolation from CLL14)	Ibrutinib (Hazard ratio of 0.66 applied to VenG extrapolation)	ERG Clinical Expert Prediction (same for both treatments)	VenG (1 knot hazard spline, independent)	Ibrutinib (Hazard ratio of 0.66 applied to VenG extrapolation)
5 year	[redacted]	[redacted]	10%	[redacted]	[redacted]
10 year	[redacted]	[redacted]	0%	[redacted]	[redacted]
20 year	[redacted]	[redacted]	0%	[redacted]	[redacted]

OS					
	VenG (exponential dependent extrapolation from CLL14)	Ibrutinib (Hazard ratio of 0.84 applied to VenG extrapolation)	ERG clinical Advisor OS (same for both treatments)	VenG (1 knot hazard spline, dependent)	Ibrutinib (Hazard ratio of 0.84 applied to VenG extrapolation)
5 year	[redacted]	[redacted]	40%	[redacted]	[redacted]
10 year	[redacted]	[redacted]	10%	[redacted]	[redacted]
20 year	[redacted]	[redacted]	0%	[redacted]	[redacted]

The ERG found that the 1-knot hazard spline model produced estimates that were closer to the predictions of their clinical expert. These also predicted that patients in both arms would have a more plausible duration in the post-progression period. (Figure 9 and Figure 10). Whilst the extrapolations used by the ERG appear more plausible than those presented by the company, the lack of meaningful data informing both the VenG extrapolation and the indirect comparison to ibrutinib mean the ERG is hesitant to recommend these assumptions for consideration for decision making.

The ERG also preferred to use the 1 knot hazard dependent spline model for VenG TTNT as this predicted that later lines of therapy would be taken for [redacted] years, rather than [redacted] years as under the company's assumptions. The ERG was unable to change this duration for ibrutinib patients due to the company's approach to modelling, however any improvement would only increase the costs of later line therapy associated with ibrutinib which were underestimated, suggesting any estimate of cost-effectiveness of VenG may be conservative. In both ERG and company base-cases, the average time on later lines of therapy for first-line ibrutinib patients was [redacted] years.

Figure 9: Markov trace plot for VenG del(17p)/TP53 mutation patients under ERG assumptions.

Figure 10. Markov trace plot for ibrutinib del(17p)/TP53 mutation patients under ERG assumptions.

Summary

A summary of the ERG's preferred assumptions for the modelling of time-to-event outcomes in the non-del(17p)/TP53 mutation and del(17p)/TP53 mutation populations can be found in Table 29 and Table 30, respectively.

Table 29: ERG's preferred assumptions in relation to time-to-event outcomes in non-del(17p)/TP53 mutation population.

Outcome	Company Base Case for non-del(17p)/TP53 mutation	ERG Base Case for non-del(17p)/TP53 mutation
PFS	Independent log-logistic extrapolation of CLL14 data	Independent 2-knot hazard spline extrapolation of CLL14 data
TTNT	Independent log-logistic extrapolation of CLL14 data	Hazard ratio between TTNT and PFS calculated from recreated CLL14 data applied to ERG PFS extrapolation.
OS	Used OS exponential extrapolation of GClb data from CLL14 for both arms	Used exponential model fitted to IPD from ERIC study to extrapolate beyond 3 years from CLL14 data.
TOT	Data from CLL14 capped at 12 months	Same as company

Table 30: ERG's preferred assumptions in relation to time-to-event outcomes in del(17p)/TP53 mutation population.

Outcome	Company Base Case for del(17p)/TP53 mutation	ERG Base Case for del(17p)/TP53 mutation
PFS	Independent log-logistic extrapolation of CLL14 data and hazard ratio for ibrutinib	Independent 1-knot hazard spline extrapolation of CLL14 data and hazard ratio for ibrutinib
TTNT	Independent log-logistic extrapolation of CLL14 data	Dependent 1 knot hazard spline extrapolation of CLL14 data
OS	Used OS exponential extrapolation of VenG data from CLL14 and hazard ratio for ibrutinib	Dependent 1-knot hazard spline extrapolation of CLL14 data and hazard ratio for ibrutinib
TOT	Data from CLL14 for VenG and equal to PFS for ibrutinib	Same as company

5.2.7 Health related quality of life

5.2.7.1 Health state utility values

Estimates of HRQoL included in the economic model were drawn from two main sources: the available literature and the CLL14 trial. Estimates from the literature were used in the company's main analyses, whereas estimates from CLL14 were used in scenario analyses.

Health status descriptions, key component for constructing preference-based health-related quality of life (utility) indices, were collected as part of the CLL14 trial using the EuroQol EQ-5D-3L instrument. Two models, one that included time as a covariate and one that did not, were used to estimate utility values from the latest available CLL14 data (August 2019 data cut-off). In the CS addendum clarification response B1, values are given for the populations with and

without del(17p)/TP53 mutation; however, these values relate only to the PFS state and were not treatment-arm specific. Utility values based on CLL14 data reported in the CS addendum clarification response B1 are given in Table 31.

Table 31. Estimated PFS utility values from CLL14 (August 2019 data cut-off)

	With del(17p)/TP53	Without del(17p)/TP53
Model 1*	[redacted]	[redacted]
Model 2 (with time) **	[redacted]	[redacted]
*Derived from $U_{it}= \alpha+\beta_1 txarm_i+\beta_2 age_i+ \beta_3 sex_i+\varepsilon_{it}$		
** Derived from $U_{it} = \alpha + \beta_1 txarm_i + \beta_2 age_i + \beta_3 sex_i + \beta_4 cycle_t + \varepsilon_{it}$		

PFS: progression-free survival.

Table 32 (Table 6 in the CS addendum clarification response B2) shows EQ-5D scores derived from data collected in CLL14 (August 2019 data cut) at different states (baseline, pre and post progression) by mutation status categorisation and treatment arm. It must be noted that values for GClb patients in the del(17p)/TP53 mutation population (3rd column in the Table) is irrelevant to this decision problem, as GClb is not an investigated comparator in this sub-population. The value set ('tariff') used to translate status descriptions to preference-based indices is not stated implicitly, but it is assumed that this was the time-trade-off based UK specific value set for EQ-5D-3L.[39]

Table 32: EQ-5D utility values from CLL14 trial (August 2019 data cut-off)

EQ-5D scores in CLL14	With del(17p)/*TP53*		Without del(17p)/*TP53*	
	VenG	GClb	VenG	GlCb
Baseline (Cycle 1 Day 1)				
Number of responses/patients that responded	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free				
Number of observations	[redacted]	[redacted]	[redacted]	[redacted]
Number of eligible patients to respond	[redacted]	[redacted]	[redacted]	[redacted]
Mean value (Standard error)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression				
Number of observations	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients that responded	[redacted]	[redacted]	[redacted]	[redacted]

Mean value (Standard error)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: European Quality of Life 5 Dimensions; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

While a large proportion of CLL14 trial participants contributed HRQoL data at baseline and at points in time before progression, only a small number of patients recorded in the available dataset (August 2019 data cut) had progressed, thus HRQoL estimates for the post-progression state are subject to considerable uncertainty. The company noted that differences between arms are not statistically significant across populations, as p-values of the treatment arm coefficient were consistently above 0.05 in all regression analyses of the CLL14 EQ-5D-3L data. The ERG agrees that, in light of the reported results, it is sensible that the base-case analysis is based on non-treatment-specific utility values.

Based on advice from clinical and health economic experts at an AbbVie-organised advisory board, the company argued that utility values from the CLL14 trial were unfeasibly high, as they exceeded the age and gender-matched values for the general population (70-year old - female 0.77, male 0.79). Thus, rather than using CLL14 data, a decision was made to use PFS and PPS health state utilities from published sources. The ERG considers the rationale for not using the unexpectedly high utility values from CLL14 to be reasonable and in line with arguments previously accepted in a previous CLL-related appraisal.[32]

A SLR was carried out (conducted in December 2018 and updated in July 2019) to identify relevant HSUVs in patients with previously untreated CLL (discussed in Section 5.1 above). According to the CS and the company's subsequent answers to a request for further clarifications, only three[40-42] of the identified publications in the HRQoL-specific SLR reported EQ-5D values. All three publications report on the same study, Connect CLL. HRQoL data in this study were collected from US individuals and the exact EQ-5D value set used to derive utility indices is not reported. The ERG considers that it is unlikely that a UK values set was used to derive utilities and agrees that these studies are very unlikely to be in line with the NICE reference case.

Given the above, the company sought an alternative source of utility values for the previously untreated CLL population and opted to use values from NICE TA343[32] as these have previously been accepted as plausible by NICE. While the original CS (and the original CS model) did not use separate utility values for different treatment status within health states, the company amended their approach and provided a new analysis that was based on using separate utility

values within the PFS health state to take into account patients' HRQoL while they are on and off treatment. The utility values used in the company's base-case analysis are presented in Table 33 below.

Table 33. New utility values suggested in the company's response to ERG's clarification questions

Progression stage	Utility value	Source	Rationale for change/use
Pre-progression IV	0.670	TA343 for PFS under IV treatment	VenG and GClb include IV treatment. This is applied for the fixed treatment duration of 12 months in the PFS state.
Pre-progression off treatment	0.820	TA343 for PFS after initial treatment is completed (0.82)	VenG and GClb should not be taking into account IV disutility for the complete time on PFS health state. A value higher than that of pre-progression oral treatment (0.71) treatment but lower than that of perfect health is a more suitable option.
Pre-progression oral treatment	0.710	TA343 for PFS under oral treatment	A utility value reflective of oral treatment should be applied for the Ibrutinib arm PFS state.
Post-progression	0.600	TA343: weighted average of the following utilities (progression after first-line treatment, PFS ± second-line treatment, relapsed line of treatment)	Used as base case and aligned with what has been accepted in previous NICE CLL appraisals.[32]

These values, which have been previously used in the economic model submitted as part of TA343 (obinutuzumab in combination with chlorambucil for previously-untreated chronic lymphocytic leukaemia)[32], were obtained from a utility elicitation study carried out by Roche®. The study aimed to derive societal preferences for QoL associated with CLL and involved eliciting utility scores from 100 members of the public for nine health states descriptions (vignettes).[32] It must be noted that the ERG which undertook TA343 considered the data from the Roche® study to be of low quality, as HRQoL was not elicited directly from patients using a generic questionnaire, such as the EQ-5D. In particular, while the ERG accepted that in the absence of a better quality of life data, Roche's study should inform the utility values, they raised a concern about the utility value of 0.82 used for progression-free patients when off treatment, as this was higher than the age-adjusted values for members of the UK general public (in the particular case, 0.76). The ERG suggested that a utility of 0.76 should be seen as an upper bound.

The ERG believes that including utility values for sub-states is appropriate; however, we question the value chosen for PFS utility off treatment, which has been criticised and retracted in TA343[32] and contradicts the rationale that CLL patients are unlikely to have better quality of life than non-CLL patients of the same age and gender in the general population. Thus, the ERG's preferred approach is to cap the value for the 'PFS, off treatment' sub-state to the gender-weighted, age-specific value for members of the UK general public. To estimate this value, the ERG followed a simple approach, based on the formula for calculating utility (EQ-5D) values in the general population published by Ara and Brazier.[43] The same formula has been used in the CS for the calculation of age adjusted general population values.

$$General\ Population\ index = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 * age^2$$

The 'PFS, off treatment' value applies after patients on VenG and GClb therapies have completed their first line treatment. Given that in these therapies first line treatment is provided over a fixed duration of approximately 12 months, the ERG estimated the utility value for a 72-year-old (i.e. starting age of 71 years plus 12 months of treatment) member of the general population, calculated according to the male/female population split in the company's submission. This value was estimated to be 0.7703. It is likely that the true value for the utility in PFS after treatment will be lower than this value, though in the absence of specific data, the ERG has adopted this pragmatic approach, which is in line with the approach taken in TA343 appraisal.[32]

A number of sensitivity and scenario analyses using alternative utility values were presented in the original CS (CS Section B.3.8.). Additional analyses were provided in response to the ERG's requests. These included scenario analyses using the treatment arm specific progression-free and post-progression utility values calculated from the CLL14 trial (original CS clarification response B3) and alternative utility values for PFS and PPS retrieved from the literature (original CS clarification response B5). In general, the results showed little change in the magnitude of the incremental effects in both sup-populations of interest and no change in direction compared to the base-case analysis results. However, when using the per arm 'progression free' and 'post-progression' utilities calculated from the CLL14 trial (August 2019 data cut), the difference in quality-adjusted life years (QALYs) between VenG and GClb in the non-del(17p)/TP53 mutation population is reduced substantially as compared to the base-case results.

5.2.7.2 Disutility due to adverse events

The expected impact of adverse events (AEs) on patients' quality of life was accounted for by combining utility AE specific utility decrements (disutilities) with duration estimates reflecting the period of time over which each AE is anticipated to affect a patient's HRQoL. Multiplying the disutility value per adverse event by the duration of the AEs gave a QALY decrement which was applied to the first cycle in the model. Disutility values were sourced from previous NICE technology appraisals and existing literature; these are presented in Table 34 (reproducing original CS Table 47). The ERG considers the evidence used to be robust and the sources of this evidence appropriate. Exploratory analyses carried out by the ERG showed disutility values and the calculated QALY decrements to have a very small impact on incremental QALYs and overall cost-effectiveness results. While second line treatment disutilities due to AEs were not included, these omissions are expected to have an inconsequential impact on the difference in QALYs between the compared treatments.

Table 34: Disutility values and QALY decrements due to adverse events

AE	Disutility (positive)	SE	Duration (days)	SE	QALY decrement	Reference
Asthenia	0.115	0.012	35.33	3.54	0.011	NICE appraisal TA306;[44] Lloyd et al. 2006;[45] PIX301 trial
Diarrhoea	0.080	0.005	3.50	0.35	0.001	NICE appraisal TA216;[46] Beusterien 2010;[47] NICE appraisal TA344[48]
Dyspnoea	0.103	0.010	12.70	1.27	0.004	NICE appraisal TA306; [44] Lloyd et al. 2006; [45] PIX301 trial
Febrile neutropenia	0.150	0.015	3.50	0.35	0.001	Lloyd et al. 2006;[45] NICE appraisal TA344[48]
Infusion related reaction	0.200	0.020	3.50	0.35	0.002	NICE appraisal TA344[48]
Leukopenia	0.090	0.009	14.00	1.40	0.003	Assumed to be the same as neutropenia; PIX301 trial
Neutropenia	0.090	0.002	3.50	0.35	0.001	Nafees et al. 2008;[49] NICE appraisal TA344[48]
Pneumonia	0.195	0.004	18.21	1.82	0.010	Tolley et al. 2013;[50] NICE appraisal TA359[51]
Sepsis	0.195	0.004	7.00	0.70	0.004	Tolley et al. 2013; [50] UK NHS Adboard
Thrombo-cytopenia	0.108	0.011	23.20	2.32	0.007	Tolley et al. 2013; [50] NICE appraisal TA359[51]

Abbreviations: AE: adverse event; QALY: quality-adjusted life year; SE: standard error.

5.2.8 Resources and costs

The following key categories of resource use and costs have been included in the company's analysis: (i) intervention and comparators' costs (including treatment acquisition and administration costs, routine care costs, tumour lysis syndrome monitoring costs and subsequent treatment costs), (ii) costs related to adverse events, and (iii) terminal care costs.

5.2.8.1 Intervention and comparators' costs

Unit costs of drugs comprising VenG and its comparators were sourced from the British National Formulary (BNF) online database.[52] An overview of the treatment regimens modelled in the analysis, as well as the drug acquisition cost (per pack size and per mg) are reproduced in Table 35 and Table 36, respectively (reproducing original CS Tables 50 and 49).

Table 35. Treatment regimens for VenG and comparators.

Regimen	Drug	Admin	Dosing schedule	Cost per cycle	Trial name (Reference)
VenG	Venetoclax	Oral	Venetoclax: • 20 mg daily during Cycle 1, Days 22–28 • 50 mg daily during Cycle 2, Days 1–7 • 100 mg daily during Cycle 2, Days 8–14 • 200 mg daily during Cycle 2, Days 15–21 • 400 mg daily during Cycle 2, Days 22–28 and on Days 1–28 for all subsequent cycles until the end of Cycle 12	Cycle 1, Days 22–28: £59.87 Cycle 2, Days 1–7: £149.67 Cycle 2, Days 8–14: £299.34 Cycle 2, Days 15-21: £598.68 Cycle 2, Days 22–28: £1,197.37 Cycle 3–12: £4,789.47	CLL14 [7]
	Obinutuzumab	IV	• 100 mg on Day 1 and 900 mg on Day 2 (or 1000 mg on Day 1) • 1000 mg at Cycle 1, Day 8 and Day 15 • 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6	£9,936 for Cycle 1 £3,312 for Cycle 2–6	CLL14 [7]
GClb	Obinutuzumab	IV	• 100 mg on Day 1 and 900 mg on Day 2 (or 1000 mg on	£9,936 for Cycle 1	CLL14 [7]

			Day 1) • 1000 mg at Cycle 1, Day 8 and Day 15 • 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6	£3,312 for Cycle 2–6	
	Chlorambucil	Oral	0.5 mg/kg at Day 1 and Day 15 for Cycles 1–12	Assuming a weight of 76: £64.79	CLL14 [7]
Ibr	Ibrutinib	Oral	420 mg daily continuously (until evidence of progressive disease or no longer tolerated by the patient)	£4,292	RESONATE [53]
Abbreviations: GClb: chlorambucil with obinutuzumab; Ibr: ibrutinib; IV: intravenous; VenG: venetoclax with obinutuzumab.					

Table 36. Drug costs for venetoclax and comparators

Drug	Dose per tablet or vial	Units per package	Cost per package	Price per mg	Source
Venetoclax Tablet, mg	10 mg	14	£59.87	£0.43	BNF [52]: Venclyxto (AbbVie Ltd)
	50 mg	7	£149.67	£0.43	
	100 mg	7	£299.34	£0.43	
	100 mg	14	£598.68	£0.43	
	100 mg	112	£4,789.47	£0.43	
Obinutuzumab, IV, mg/ml	1000mg	1	£3,312.00	£3.31	BNF[52]: Gazyvaro 1000mg/40ml concentrate for solution for infusion vials (Roche Products Ltd)
Chlorambucil, Tablet, mg	2 mg	25	£42.87	£0.86	BNF[52]: Chlorambucil 2mg tablets (Alliance Healthcare (Distribution) Ltd)
Ibrutinib, Tablet	140 mg	90	£4,599.00	£0.37	BNF[52]: Imbruvica 140mg capsules (Janssen-Cilag Ltd)
	140 mg	120	£6,132.00	£0.37	
Abbreviations: BNF: British National Formulary; IV: intravenous.					

The original CS stated that there is a simple discount patient access scheme (PAS) for venetoclax which entails providing a discount of [redacted] on the list price for venetoclax.

5.2.8.2 Administration costs

Administration costs were included in the model for the intravenously-delivered treatments obinutuzumab and rituximab (subsequent treatment) (Table 51 in the original CS, reproduced as Table 37 below). Cost calculations for treatment administration accounted for the cost of pharmacist time for dispensing the IV drugs.[54] Alternative delivery methods (standard IV, rapid IV and subcutaneous administration) were also considered. Some assumptions were employed to enable calculations, including: (i) that the cost of a rapid infusion would be similar to a simple chemotherapy delivery included in the NHS reference costs, and (ii) that rituximab containing treatment (VenR) uses a 30:70 ratio between standard and rapid IV infusions. The latter was justified on the basis of a survey exploring administration policies that was conducted in 20 UK trusts. The administration cost assigned to obinutuzumab was that of a standard IV infusion.

Table 37. Drug administration costs.

Drug	Cost	Currency code	Description
IV standard	£298.53 (= £289.33 + £9.20)	SB15Z	IV administration cost from NHS Reference Costs 2017-18; Total HRGs, SB15Z: deliver subsequent elements of a chemotherapy cycle. This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.20).
Rituximab (IV Rapid)	£238.19 (= £228.99 + £9.20)	SB12Z	IV administration cost from NHS Reference Costs 2017-18; Total HRGs, SB12Z: deliver Simple Parenteral Chemotherapy at First Attendance. This is supplemented by the cost of pharmacist time for dispensing the IV drugs (£9.20).
Abbreviations: IV: intravenous; HRG: Healthcare Resource Group; NHS: National Health Service.			

The ERG considers the methods and assumptions employed in calculating administration costs to be reasonable. Sensitivity analyses using alternative values for administration cost inputs (costs, split between rapid and standard infusion) demonstrated a very small impact on total incremental costs and overall cost-effectiveness results.

5.2.8.3 Routine care and monitoring costs

A range of health care resources associated with the pre-progression and post-progression states were included in the cost calculations. These included scans, blood tests, transfusions and consultations and were informed by discussion with clinicians at an AbbVie-organised advisory board. While the clinical expert supporting the ERG considered the type and frequency of care comprising the annual resource use reasonable, the ERG identified some discrepancies in categories of routine care included and annual frequency of use between this and a previous

submission (TA561[34]). Values for both submissions are given in Table 38 below. Checks carried out by the ERG using the categories and values specified in TA561[34] led to a small increase in the difference in total costs between treatments in favour of VenG.

Table 38. Pre- and post-progression annual resource use frequency

Resource/procedure	TA 561 [34]		CS, Table 52	
	Annual pre-progression frequency	Annual post-progression frequency	Annual pre-progression frequency	Annual post-progression frequency
Full blood count	4	8	4	4
LDH test	2	0	2	2
Chest x-ray	0	2	0	-
Bone marrow exam	0	1	0	-
Haematologist visit	2	6	4	4
Inpatient non-surgical medical stays	0	4	0	3
Nurse home visit	-	-	-	-
Full blood transfusion	0	11	0	1
Biochemistry test: renal - Urea and electrolytes test	-	-	3	2
Biochemistry test: liver function test	-	-	3	2
Immunoglobulins Blood Test	-	-	3	2

Abbreviations: CT: computerised tomography; LDH: lactate dehydrogenase.

National reference costs available for the most recent year (2017/18)[55] were used to inform the routine care and monitoring costs. These are given in Table 39 (reproducing original CS Table 53).

Table 39: Routine care and monitoring costs used in the model

Routine care and monitoring costs	Value	HRG codes from reference costs 2017/18[555552525355]
Full blood count	£2.51	DAPS05- Haematology
LDH	£1.11	DAPS04 - Clinical biochemistry
Haematologist visit	£159.65	Outpatient Attendances Data: 303- Clinical haematology
Inpatient non-surgical/medical visit	£572.78	National schedule of reference costs 2017/18: Weighted average of day case, Chronic Lymphocytic Leukaemia, including Related Disorders, SA32A (£396), SA32B (£428), SA32C (£379) and SA32D (£449) = £432.93

		PSSRU 2018: Medical consultant hour (£108) + qualification costs (£31.846) = £139.846
Full blood transfusion	£187.97	Outpatient Procedures- 303, Clinical Haematology, single plasma exchange or other intravenous blood transfusion, 19 years and over (SA44A)
CT Scan	£92.81	Weighted average of RD20A (£88) and RD21A (£106)[29]
Biochemistry test: renal - Urea and electrolytes test	£1.11	DAPS04 – Clinical biochemistry
Biochemistry test: liver function test	£1.11	DAPS04 - Clinical biochemistry
Immunoglobulins Blood Test	£2.51	DAPS05- Haematology (assumed to be equal to full blood count)
Abbreviations: CT: computerised tomography; HRG, Healthcare Resource Group; LDH, Lactate Dehydrogenase; PSSRU, Personal Social Services Research Unit.		

5.2.8.4 Treatment-specific monitoring costs – Tumour lysis syndrome

CLL patients are at increased risk of tumour lysis syndrome (TLS), a condition that occurs when a large number of cancer cells die within a short period. TLS is most commonly observed in patients with hematologic malignancies and, although the risk of TLS in CLL is deemed to be small[56], developing the condition can have a significant impact on health and economic outcomes. Thus, the expected cost of TLS prophylaxis was calculated and included in the model. Calculations were based on an algorithm that categorised patients according to risk of developing TLS based on data from the treated CLL14 population (August 2019 data cut-off).

In brief, patients were divided into those at lower and greater risk based on tumour mass and absolute lymphocyte count (ALC) (i.e. lower risk: lymph node with a diameter ≤5 cm and ALC <25 x 10^9/L; greater risk included all other patients). This resulted in [redacted] of patients on VenG and [redacted] patients on GClb being included in the lower risk group, and 86.57% of patients in the VenG arm and 87.96% of patients in the GClb arm being part of the greater risk group. The greater risk group was subdivided into two groups according to creatinine clearance.

The TLS risk group distribution and the cost by risk of tumour burden can be seen in Table 40 and Table 41, reproducing Tables 32 and 33 in CS addendum.

Table 40. TLS risk distribution for VenG and GClb treatment arms

Treatment	Lower Risk (node diameter ≤5 cm and ALC <25 x 10^9)	Greater Risk (node diameter >5 cm or ALC >25 x 10^9)	
		Creatinine clearance > 80 mL/min	Creatinine clearance ≤ 80 mL/min
VenG	[redacted]	[redacted]	[redacted]
GClb	[redacted]	[redacted]	[redacted]

Abbreviations: ALC: absolute lymphocyte count; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

Table 41: TLS cost split by tumour burden in each treatment arm.

Treatment	Low tumour burden	Greater Risk (CrCl >80)	Greater Risk (CrCl >80)	Total cost used in model
VenG	£1,411	£1,708	£2,230	£1,784
GClb	£1,411	£1,489	£2,242	£1,629

Abbreviations: CrCl: creatinine clearance; GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab.

According to calculations based on the TLS risk classification and the prophylaxis algorithm, the cost of TLS prophylaxis applied in the first cycle of the model to the VenG arm and GClb is £1,784 and £1,629 respectively. The company stated that the cost is lower in the GClb arm as there are fewer high-risk patients in the GClb arm compared to the VenG arm. This appears to favour GClb and is therefore a conservative assumption for VenG. The TLS costs of the venetoclax regimens were halved, doubled and removed in scenario analyses. The ERG believes that the approach and inputs used in the TLS prophylaxis calculations is reasonable and broadly in line with previously submitted evidence for TA561.[34] Checks carried out by the ERG confirmed the company's assertion that these costs have a small impact on overall cost-effectiveness.

5.2.8.5 Subsequent treatment costs

Subsequent treatment costs were calculated according to the type of subsequent treatment mix received, the point in time when subsequent treatment would be initiated and the length of time over which subsequent treatment would be administered.

The company determined the type of treatment mix offered to patients after first line treatment by consulting UK-based clinical experts. Subsequent treatments included in the economic

model, stratified by population (with and without del(17p)/TP53 mutation) and first line treatment (VenG, GClb, ibrutinib) are reproduced in Table 42. Clinical expert advice sought by the ERG confirmed that these treatments are consistent with what is offered in UK clinical practice. The ERG's clinical expert added that venetoclax with rituximab (VenR) is becoming increasingly more popular as a subsequent treatment for patients who had VenG or GClb as first line treatment, as offering VenR instead of ibrutinib means that the option of offering ibrutinib remains available, should it be needed as a further treatment. Our expert indicated that a reasonable expectation would be that, in the future, about 20% of patients would be offered ibrutinib after first line treatment, and 80% would be offered VenR. However, a change in these proportions has a minimal effect on overall incremental results.

Table 42. Overview of base case subsequent treatment mix

Initial treatment	**Subsequent treatment**	
	Non-del(17p)/*TP53* mutation	**del(17p)/*TP53* mutation**
VenG	50% ibrutinib; 50% VenR	100% ibrutinib
GClb	50% ibrutinib; 50% VenR	N/A
Ibrutinib	N/A	100% venetoclax monotherapy
Abbreviations: GClb: chlorambucil with obinutuzumab; VenG: venetoclax with obinutuzumab; VenR: venetoclax with rituximab.		

The median length of time (in months) over which subsequent treatment is received were sourced from recent published literature identified through a systematic review (Table 43).

Table 43: Subsequent treatment durations used in the model

Subsequent treatment	**Median duration, months**	**Source**
VenR	24.4	Kater et al. (2019) [57]
Ibrutinib	39.00	O'Brien et al. (2018)[58]
Venetoclax monotherapy	16.00	Davids et al. (2018) [59]
Abbreviations: VenR: venetoclax with rituximab.		

Together with the treatment mix and split in Table 42 above, these lengths were used to calculate the average treatment acquisition cost per cycle over the subsequent treatment period. The point in time at which eligible patients would receive subsequent treatment was estimated according to the TTNT curves for VenG and GClb after these were adjusted for overall survival from the CLL14 trial.

A different approach was used in estimating subsequent treatment costs for ibrutinib in the del(17p)/TP53 mutation population. There, the proportions of patients who receive subsequent treatment and are still alive was obtained based on the PPS and OS curves. The company justified the use of a different approach by explaining that publicly available patient level data to inform TTNT curves for ibrutinib could not be identified.

5.2.8.6 Adverse reaction unit costs and resource use

An overview of adverse event costs was given in CS, Table 61 (partially reproduced in Table 44 below). The company stated that these were aligned with the accepted costs used in TA561, with minor changes made to the costs for neutropenia, leukopenia, diarrhoea, and sepsis according to clinical feedback at an AbbVie-organised advisory board. The ERG found no further information in the original CS about the reasons for these changes.

Table 44. Adverse event cost overview

Adverse event	Cost	Source
Asthenia	£657.76	TA498: National Schedule of Reference Costs 2017-18, PSSRU 2018[60]
Diarrhoea	£0.34	TA344[48] Woods et al. (2012)[61]
Dyspnoea	£591.49	NHS Reference Costs 2017-18. Total - HRGs, Other Respiratory disorders without interventions (weighted average of DZ19L-DZ19N [£1,132], DZ19M [£725] and DZ19N [£475])[62]
Febrile neutropenia	£6,563.61	NICE TA359: NHS Reference Costs 2012-13; Inflated by four years using the PSSRU HCHS index (£5993.03*1.026*1.019*1.022*1.025).[62]
Infusion related reaction	£432.93	NHS reference costs 2016-2017. Weighted average of day case, Chronic Lymphocytic Leukaemia, including Related Disorders, SA32A (£396), SA32B (£428), SA32C (£379) and SA32D (£449).
Leukopenia	£535.56	Same as neutropenia
Neutropenia	£535.56	Cost of lenograstim for 8 days (median duration of neutropenia in MURANO trial - Seymour et al. 2018)[63]
Pneumonia	£6167.48	NHS Reference Costs 2017-18[55]
Sepsis	£6167.48	Same as pneumonia
Thrombocytopenia	£640.09	NHS Reference Costs 2017-18[55]
Abbreviations: BNF: British National Formulary; HCHS: hospital and community health services; HRG: Healthcare Resource Group; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.		

The ERG checked these costs and compared them with AE related costs used in TA561.[34] These are presented in Table 45.

Table 45. AE costs in current appraisal and TA561

Adverse event costs	Current appraisal (CS)	TA561[34]
Asthenia	£657.76	-
Diarrhoea	£0.34	-
Dyspnoea	£591.49	-
Febrile neutropenia	£6,563.61	-
Infusion related reaction	£432.93	-
Leukopenia	£535.56	-
Neutropenia	£535.56	£119.49
Pneumonia	£6,167.48	£6,149.58
Sepsis	£6,167.48	-
Thrombocytopenia	£640.09	£621.34

Between the two submissions, there is a discrepancy in the unit costs for neutropenia, though replacing the value used in the economic model by that accepted in TA561 had a negligible effect on total and incremental costs.

5.2.8.7 Miscellaneous costs

Costs associated with terminal care were calculated and included in the model in the same way as in NICE appraisal TA561.[34] Briefly, terminal care costs were applied to all patients who transition to the death health state as a one-off cost and came from a published study on end-of-life care for solid tumour cancer patients[64] on the basis that the costs of terminal care would be similar between solid tumour and haematology patients. The mean total cost due to terminal care was estimated to be £6,662. No costs related to specific health-states were included in the economic analysis; NHS and Personal Social Services costs accruing over the course of the modelled time horizon are included in the categories above.

5.2.9 Cost-effectiveness results

The company presented base-case results generated from the economic model for the two populations of interest:

- Patients with previously untreated CLL, without del(17p)/TP53 mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR.
- Patients with previously untreated CLL, with del(17p)/TP53 mutation.

Results for two different pricing arrangements were provided: i) list price for VenG vs list price of all comparators (GClb and ibrutinib), and ii) PAS price for venetoclax only (obinutuzumab remains at list price) vs list price of all comparators (GClb and ibrutinib). For brevity, and after

discussion with the NICE Technical Team for this appraisal, it was established that a PAS discount applied to venetoclax only provides uninformative results, the focus in the remainder of this report is on the analyses based on list prices for all treatments. The ERG has produced a confidential addendum reporting cost-effectiveness results calculated based on the venetoclax PAS discount and the confirmed PAS discounts for obinutuzumab and ibrutinib.

In general, the company's preferred base-case analysis suggests that VenG is associated with a greater number of QALYs and lower costs against its comparator in the non-del(17p)/TP53 mutation population, suggesting that VenG is dominant versus GClb. In the del(17p)/TP53 mutation population, VenG resulted in a lower average number of QALYs and lower costs versus ibrutinib. In both cases, VenG resulted in a large, positive net monetary benefit (NMB) at both the £20,000 and £30,000 per additional QALY willingness-to-pay (WTP) thresholds (Table 46).

The company stated that, in the non-del(17p)/TP53 mutation population, cost-effectiveness is largely driven by the superior progression-free survival associated with VenG, and lower subsequent costs following progression for VenG compared to GClb. In the del(17p)/TP53 mutation population, a key driver of the cost-effectiveness results is the much higher treatment costs due to ibrutinib being offered over a non-fixed and typically long period of time (i.e. until patients' progress) in contrast to VenG, which is provided for a fixed number of cycles. Results calculated on the basis of PAS for venetoclax only (not presented here) were of the same magnitude and direction.

Table 46: Company's base case results at list prices

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Non-del(17p)/*TP53* mutation population							
GClb	[redacted]	6.742				[redacted]	[redacted]
VenG	[redacted]	7.799	[redacted]	1.057	[redacted]		
Del(17p)/*TP53* mutation population							
Ibrutinib	[redacted]	4.153				[redacted]	[redacted]
VenG	[redacted]	3.991	[redacted]	-0.163	[redacted]		

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab; WTP: willingness to pay.
*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold. Positive NMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.

5.2.10 Sensitivity analyses

Various types of sensitivity analyses, including probabilistic, deterministic and scenario analyses, were undertaken by the company.

5.2.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were carried out by assigning distributions to a range of uncertain parameters and randomly sampling from these distributions over 1,000 replications. Information about the type of distributions used can be found in the CS original and addendum models. The company stated that, in cases where uncertainty estimates for parameters were unavailable, the analysis employed a variability (i.e. standard error) estimate of 10% of a parameter's mean value. Clarifications were sought by the ERG about the rationale for using the same standard error (typically 10% of a parameter's mean value) uniformly across parameters as diverse as resource use, probability of events, unit costs and utility values (original CS clarification response B7). In addition, the ERG questioned the fact that uncertainty around the OS and PFS hazard ratios for ibrutinib were set to 10% of the mean despite the fact that more accurate uncertainty values for these parameters were available. In response, the company made changes in the uncertainty values (standard errors) assigned to the hazard ratios mentioned above. The company made no changes to standard errors attached to utility values citing lack of information required for the calculation of appropriate values.

Results of the probabilistic sensitivity analyses generated in the CS addendum model for the comparison between i) VenG and GClb in the population without del(17p)/TP53 mutation and ii) VenG and ibrutinib in the population with del(17p)/TP53 mutation are given below (Figure 11 to Figure 14). As before, for all these comparisons, all medications costs, including those for venetoclax, were kept at list prices.

Figure 11: Scatter plot of probabilistic results on the cost-effectiveness plane for non-del(17p)/TP53 population – list prices

Figure 12: Cost-effectiveness acceptability curves for non-del(17p)/TP53 population – list prices

Figure 13: Scatter plot of probabilistic results on the cost-effectiveness plane for del(17p)/TP53 population – list prices

Figure 14: Cost-effectiveness acceptability curves for del(17p)/TP53 population – list prices

5.2.10.2 Deterministic sensitivity analyses

The company carried out a number of one-way sensitivity analyses to identify key model drivers and important sources of uncertainty. In each of these analyses, the central estimate of each base-case parameter was replaced by low and high estimates. Tornado plots showing the first ten uncertain parameters whose impact on the incremental cost-effectiveness ratio (ICER) is the greatest can be seen in Figure 15 and Figure 16 for VenG vs GClb and VenG vs ibrutinib, respectively.

For the comparison between VenG and GClb, the one-way sensitivity analysis calculations suggest that the parameter with the greatest impact on the ICER is the PFS utility value following IV treatment (utility for PFS: Post fixed treatment duration (FTD) IV treatment). Whereas, for the comparison between VenG and ibrutinib, the parameter with the greatest impact on the ICER is the PFS utility value at the time of the FTD period (utility for PFS: FTD IV treatment). While, these one-way sensitivity analyses offer indications on the influence of single parameters on the cost-effectiveness results, these should be seen as 'stress tests' where the lower and upper values substituting a parameter may not be realistic. It must also be noted that one-way sensitivity analyses do not account for interrelations between parameters or the fact that more than one of the parameters will be uncertain at the same time.

Figure 15. Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus GClb) for non-del(17p)/TP53 mutation population – list prices.

Figure 16. Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus ibrutinib) for del(17p)/TP53 mutation – list prices.

5.2.10.3 Scenario analyses

Alternative values for various parameters were considered in the company's scenario analyses. Indicatively, scenarios tested included different discount rates, time horizons, exclusion of TLS prophylaxis costs, various utility values from different sources, different survival models based on a range of distributions for VenG and extreme value scenarios related to the specification of PFS and OS curves. A full list of the variables and approaches subjected to scenario analysis are available in the CS, Table 69. Results of scenario analysis were updated to reflect the most recently available data cut (August 2019) and were summarised in CS addendum (Table 40 for the non-del(17p)/TP53 population and in Table 41 for the del(17p)/TP53 population).

Scenario analyses pertaining to the non-del(17p)/TP53 population suggested that VenG is consistently less costly and more effective when compared to GClb. An exception to this was when the time horizon of the analysis was limited to 5 years. Analyses related to the del(17p)/TP53 population showed that VenG resulted in lower costs and lower QALYs, and an overall positive NMB in all but two scenarios (i.e. when equivalent OS and PFS were assumed and time horizon was limited to 5-years. In these cases, VenG was dominant versus ibrutinib).

As discussed above, additional analyses run in response to the ERG's requests included: (i) a scenario where utility values used in the model are treatment-specific values obtained from the CLL14 trial (August 2019 data cut) (Table 47) and (ii) a scenario where Clb is administered over six cycles, which is typically the case in UK clinical practice (Table 48). These analyses were provided in response to ERG queries B4 and B5 in the CS addendum clarifications, respectively.

In both analyses, results are in broad agreement with those of the company's base-case analysis. However, using utility values from CLL14 in the comparison between VenG and GClb (see Scenario 2 in Table 47) led to a significant decrease in incremental QALYs as compared to the base-case results, and a notable reduction in NMB.

Table 47: Scenario analyses undertaken using the utility values from the CLL14 trial (list prices)

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER, £/QALY	Net monetary benefit
Scenario 1: with del(17p)/*TP53* mutation VenG: PFS (IV) = [redacted], PPS = [redacted]				
Base case: with del(17p)/*TP53*	[redacted]	−0.163	[redacted]	[redacted]
Scenario 1: vs Ibrutinib	[redacted]	−0.436	[redacted]	[redacted]
Scenario 2: without del(17p)/*TP53* mutation VenG: PFS (IV and post IV*) = [redacted], PPS = [redacted] GClb: PFS (IV and post-IV*) = [redacted], PPS = [redacted]				
Base case: without del(17p)/TP53	[redacted]	1.057	[redacted]	[redacted]
Scenario 2: vs GClb	[redacted]	0.052	[redacted]	[redacted]

*The same utility value is also applied to post-IV since the literature post-IV utility value is less than the utility generated from the CLL14 trial while on IV.
**This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold. Positive NMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.

Table 48: Scenario analyses assuming GClb is administered over six cycles (list prices; efficacy remains as per CLL14)

Incremental results of VenG vs comparator	Incremental discounted costs	Incremental discounted QALYs	ICER, £ per QALY	Net monetary benefit
Scenario 1: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the CLL14 trial (0.5 mg/kg on Days 1 and 15) and efficacy based on 12 cycles as per CLL14 trial				

Base case: without del(17p)/*TP53* mutation	[redacted]	1.057	[redacted]	[redacted]
Scenario 1: vs GClb	[redacted]	1.057	[redacted]	[redacted]
Scenario 2: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the UK clinical practice dose (10 mg/m^2 on Days 1 and 15) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	[redacted]	1.057	[redacted]	[redacted]
Scenario 2: vs GClb	[redacted]	1.057	[redacted]	[redacted]
Scenario 3: without del(17p)/*TP53* mutation 6 cycles of Clb at a dose used in the UK clinical practice dose (10 mg/m^2 on Days 1 to 7) and efficacy based on 12 cycles as per CLL14 trial				
Base case: without del(17p)/*TP53* mutation	[redacted]	1.057	[redacted]	[redacted]
Scenario 3: vs GClb	[redacted]	1.057	[redacted]	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

5.2.11 Model validation and face validity check

The company took a number of reasonable steps to validate the submitted economic model. To ascertain that the model is clinically valid, AbbVie held an advisory board meeting to discuss the model structure, key model assumptions, and associated inputs with clinicians knowledgeable in CLL and health economists. Quality checks were also carried out using a pre-specified model quality check template and two health economist modellers reviewed the model and its underlying assumptions. Challenges in relation to OS extrapolation beyond the CLL14 trial period were presented to a leading CLL clinician involved with the CLL trials. Two clinical experts who had previously participated in the advisory board provided their opinion on the degree to which the outcomes are valid to help determine the external validity of the model extrapolations. The ERG believes that the above activities and approaches to model validation are appropriate.

The ERG assessed the face validity of the model, particularly with respect to suitability of the constructed structure, appropriateness of data sources and inputs, and plausibility of the obtained results. The structure of the submitted model was scrutinised in order to ascertain than no meaningful health states and pathways have been omitted. While the model is parsimonious, the ERG is satisfied that a partitioned survival model is suitable for the particular decision problem and available data, and is in line with the approach taken in previous CLL appraisals. The ERG also notes that important elements of the analysis (e.g. the adopted perspective, time horizon and discount rates) are in agreement with the NICE Reference Case.

The ERG felt that the company took reasonable steps to ascertain that evidence used in the model was rigorous and suitable. Much of the data used to populate key model parameters were obtained from relevant randomised clinical trials, particularly CLL14, and previous technology appraisals. In instances where the choice of evidence was not drawn from the CLL14 trial, the ERG felt that the evidence employed was *per se* largely appropriate (with the exception of 'pre-progression, off treatment' status). In cases where inappropriate use of evidence or errors in the calculations of input values were identified by the ERG (e.g., incorrect estimates of uncertainty around OS and PFS HR for ibrutinib) these have been queried with the company and highlighted in the critique above. The validity of various assumptions incorporated in the analysis (e.g. related to the treatment and progression pathways, information about NHS services and care routinely provided to CLL patients) was scrutinised by seeking expert opinion from the ERG's clinical expert.

The economic model, which was submitted in a spreadsheet, was also scrutinised by the ERG. Wherever possible, 'extreme value' tests were performed, by replacing the base-case value of influential variables with low and high estimates. Results were found to agree with expectations about the direction and magnitude of change in model parameters and final results. Examination of macros (VBA coding) used to perform simulations did not identify errors in the code.

In summary, the ERG believes the steps undertaken by the company to ensure the validity of the model are appropriate. Putting aside limitations in the analysis due to data immaturity and unavailability, the ERG's examinations deem the model's validity to be, on the whole, sound.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on the critique of the submitted economic model, the ERG suggests an amended base-case analysis. The rationale for these amendments has been given alongside the critique provided in Section 5.2 and is summarised below.

5.3.1 The ERG's preferred base-case analysis

Amendments were implemented to reflect the ERG's preferred base-case analysis in both the non-del(17p)/TP53 and the del(17p)/TP53 populations. These related to the following parameters:

- Utility value for 'pre-progression, off treatment' status. The ERG questions the utility value used by the company for non-progressed patients who are not on treatment. This value is higher than the age-adjusted utility value in the general population and contradicts the rationale used for the choice in utility values elsewhere in the CS, which suggests that CLL patients are unlikely to have better quality of life than their non-CLL counterparts in the general population. Thus, the ERG's preferred approach is to cap the utility value for the 'pre-progression, off treatment' status by using the gender-weighted, age-specific value for members of the UK general public (see Section 5.2.7.1).
- Time-to-event parameters and extrapolations. Changes in PFS, TTNT and OS were implemented in order to obtain extrapolations that the ERG considers more plausible and better aligned with the available data (see Section 5.2.6)

The ERG's preferred base-case values and approaches are summarised below in Table 49 and Table 50 for the populations without and with del(17p)/TP53 population, respectively. Results of the ERG base-case analysis are presented in Sections 5.5.1 and 5.5.2.

Table 49: Summary of values and approached used in the ERG's base case analysis for the non-del(17p)/TP53 population.

Parameter	Value in company's base-case analysis	Value in ERG's preferred base-case analysis	Section where justification for amendment is given
Utility value: 'pre-progression, off treatment' status.	0.82	0.77	Section 5.2.7.1
Time-to-event parameters			Section 5.2.6
PFS	Independent log-logistic extrapolation of CLL14 data	Independent 2-knot hazard spline extrapolation of CLL14 data	
TTNT	Independent log-logistic extrapolation of CLL14 data	Hazard ratio between TTNT and PFS calculated from recreated CLL14 data applied to ERG PFS extrapolation.	
OS	Used OS exponential extrapolation of GClb data from CLL14 for both arms	Used exponential model fitted to IPD from ERIC study to extrapolate beyond 3 years from CLL14 data.	

Table 50: Summary of values and approach used in the ERG's base case analysis for the del(17p)/TP53 population

Parameter	Value in company's base case analysis	Value in ERG's preferred base case analysis	Section where justification for amendment is given
Utility value: 'pre-progression, off treatment' status.	0.82	0.77	Section 5.2.7.1
Time-to-event parameters			Section 5.2.6
PFS	Independent log-logistic extrapolation of CLL14 data and hazard ratio for ibrutinib	Independent 1-knot hazard spline extrapolation of CLL14 data and hazard ratio for ibrutinib	
TTNT	Independent log-logistic extrapolation of CLL14 data	Dependent 1 knot hazard spline extrapolation of CLL14 data	

OS	Used OS exponential extrapolation of VenG data from CLL14 and hazard ratio for ibrutinib	Dependent 1-knot hazard spline extrapolation of CLL14 data and hazard ratio for ibrutinib	
TOT	Data from CLL14 for VenG and equal to PFS for ibrutinib	Same as company	

5.3.2 Additional sensitivity analyses undertaken by the ERG

As discussed in Section 5.2.10, the company carried out an extensive range of sensitivity analyses (reported in the original CS and in subsequent answers to ERG's requests for clarifications) which limited the need for additional sensitivity analyses. However, two additional scenario analyses were carried out by the ERG, where the ERG's preferred base-case amendments were altered. These involved:

- Using an alternative utility value for the progression-free, off treatment sub-state. This value was calculated on the basis of the male/female split specific to CLL patients taken from Cancer Research UK incidence statistics[3] and is applicable to both the non-del(17p)/TP53 and del(17p)/TP53 mutation populations. The value used in this sensitivity analysis is 0.773457027 (compared to 0.7703 in the ERG's base-case and 0.820 in the company's base case).
- Carrying out the ERG's preferred amendments in TTE parameters other than the change in OS for VenG, whilst maintaining the utility value of 0.820 for the progression-free off treatment substate. This was intended to explore whether VenG would remain less costly and more effective despite a decrease in the cost of subsequent treatments following first line treatment with GClb. This is applicable to the non-del(17p)/TP53 mutation population.

The results of these analyses are given in Section 5.5.2 below.

5.4 Conclusions of the cost-effectiveness section

Searches in the available literature did not identify any existing economic evaluations that could address the exact decision problem, as detailed in the final scope, for this appraisal. Thus, the company constructed a *de novo* economic model to evaluate the cost-effectiveness of VenG compared to i) GClb (in the non-del(17p)/TP53 mutation population) and ii) ibrutinib (in the del(17p)/TP53 population). A three-state partitioned survival model was presented in the CS and formed the basis for the cost-effectiveness analyses in both populations.

The company's decision problem addressed in the cost-effectiveness is largely consistent with the NICE scope, although there are some deviations related to the population in the CLL14 and exclusion of treatments (see Section 3 for critique and justifications). The analytic elements of the model (including the chosen model structure, time horizon, discounting, evaluation of costs and outcomes) are generally in line with the NICE Guide to Methods of Technology Appraisal and past NICE Technology Appraisals in CLL.[32, 34]

The immaturity of the CLL14 trial data and reliance on an unadjusted naïve indirect comparison (for VenG vs ibrutinib) add a notable layer of uncertainty to time-to-event extrapolations. Time-to-event data are drivers of incremental costs and outcomes in the decision model. Limitations in currently available data make it difficult to draw a complete and reliable picture of each treatment's effectiveness and they inevitably affect the final cost-effectiveness results. The ERG has identified extrapolations that, we believe, are more plausible and appropriate; these have been incorporated in the ERG's preferred base-case analysis.

Employed health state utility values were sourced from the literature (TA343[32]), rather than EQ-5D-3L data collected in the CLL14 trial. The justification for not using CLL14 trial—that is, the unexpectedly high EQ-5D values that exceed those of the general age-adjusted population—is considered to be reasonable. QALY decrements due to adverse events were appropriately applied. However, the ERG considers the utility value assigned to reflect the 'progression-free, off treatment' status to be problematic. An alternative value has been put forward as a more plausible estimate in the ERG's base-case analysis.

A number of NHS services and their relevant costs were identified and taken into account in cost calculations. These included acquisition and administration costs for first and second line treatments, routine care and tests, cost of TLS prophylaxis and terminal care costs. Cost components included and analytic methods used in the cost calculations are, generally, in line with previous technology appraisals in CLL.

In the company's preferred base-case analysis, and on the basis of list prices for all treatments, VenG is associated with a greater number of QALYs and lower costs against its comparator in the non-del(17p)/TP53 mutation population, suggesting that VenG is dominant versus GClb. In the del(17p)/TP53 mutation population, VenG resulted in a lower average number of QALYs and lower costs versus ibrutinib. In both cases, VenG resulted in a large, positive NMB at both the £20,000 and £30,000 per additional QALY willingness to pay thresholds. The ERG has

undertaken additional comparisons using confidential discounted prices for all treatments; results are reported in an accompanying confidential addendum.

A range of sensitivity analyses, in the form of probabilistic sensitivity analysis, deterministic sensitivity analyses (where parameter values were replaced by low and high estimates) and scenario analyses (where alternative plausible values and approaches were tested) were carried out to explore the robustness of these findings. Additional scenario analyses were also presented in response to requests from the ERG (including for a six-cycle treatment schedule for Clb, utility values derived from CLL14 and use of the CSR mutation status classification in the economic model). Overall, results are relatively robust to changes, supporting the suggestion that, given the existing state of evidence and at typically acceptable WTP threshold values, VenG is a cost-effective option in both the non-del(17p)/TP53 and del(17p)/TP53 mutation populations.

5.5 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

5.5.1 Results of the ERG's preferred base-case

The effect of the ERG's preferred base-case amendments on the cost-effectiveness results for the non-del(17p)/TP53 and del(17p)/TP53 populations are reported below. For ease of interpretation, the emphasis on cost-effectiveness estimates are placed on NMB (at a £30,000 WTP threshold and, additionally at a £20,000 WTP threshold), rather than ICERs, as results fall within quadrants of the cost-effectiveness plane where ICER values are not informative or require a different interpretation. Positive values of NMB indicating that a treatment is cost-effective at a given willingness-to-pay threshold; zero indicates equivalence and negative values indicate that a treatment is not cost-effective at the particular threshold. Presented results are calculated based on list prices and percentage changes are calculated on the basis of NMB at a £30,000 WTP per additional QALY.

5.5.1.1 ERG's base-case results for the non-del(17p)/TP53 mutation population.

The effect of the ERG's base-case amendments on the results for the non-del(17p)/TP53 mutation population, when each change is carried out one at a time, can be seen in Table 51.

A change to ERG's preferred utility value for the 'pre-progression, off treatment' status resulted in a small reduction in incremental QALYs (VenG vs GClb), leading to a decrease in the NMB by about [redacted] compared to the company's base-case results. After implementing this adjustment, the revised NMB was found to be [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively.

The effect of the ERG's changes in TTE parameters and extrapolations was more prominent. Carrying out these changes resulted in a sizeable reduction in both the difference in costs and the difference in QALYs between VenG and GClb, leading to a decrease by nearly [redacted] in the company's base case findings. In this case, the revised NMB was found to be [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively.

Table 51. Results for the non-del(17p)/TP53 mutation population when ERG's amendments are implemented one at a time (at list prices).

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Company's base-case results							
GClb	[redacted]	6.742				[redacted]	[redacted]
VenG	[redacted]	7.799	[redacted]	1.057	[redacted]		
Results based on ERG's change in utility value for 'pre-progression, off treatment' status only							
GClb	[redacted]	6.601				[redacted]	[redacted]
VenG	[redacted]	7.418	[redacted]	0.818	[redacted]		
Results based on ERG's change in time-to-event parameters and extrapolations only							
GClb	[redacted]	5.692				[redacted]	[redacted]
VenG	[redacted]	6.279	[redacted]	0.587	[redacted]		

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab; NMB: net monetary benefit; WTP: willingness to pay.

As anticipated, carrying out these ERG amendments simultaneously—that is, implementing the ERG's suggested base-case analysis—resulted in reductions in incremental costs and QALYs compared to the company's base-case values, leading to an overall reduction in NMB by approximately [redacted]. The resulting ERG's base-case NMB in the non-del(17p)/TP53 mutation population were [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively (Table 52).

Table 52. ERG's base case results for the non-del(17p)/TP53 mutation population (at list prices)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Company's preferred base-case							
GClb	[redacted]	6.742				[redacted]	[redacted]
VenG	[redacted]	7.799	[redacted]	1.057	[redacted]		
ERG's preferred base-case							
GClb	[redacted]	5.572				[redacted]	[redacted]
VenG	[redacted]	6.027	[redacted]	0.454	[redacted]		

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab; NMB: net monetary benefit; WTP: willingness to pay.

5.5.1.2 ERG's base-case results for the del(17p)/TP53 mutation population.

The effect of the ERG's base-case amendments on the results for the del(17p)/TP53 mutation population, when each change is carried out one at a time, can be seen in Table 53 below.

Using the ERG's preferred utility value for 'pre-progression, off treatment' resulted in a reduction in incremental QALYs (VenG vs ibrutinib), leading to a decrease in the NMB by about [redacted] compared to the company's base-case results. After implementing this adjustment, the revised NMB was found to be [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively.

The ERG's changes in TTE specifications resulted in a sizeable reduction in the difference in costs and a modest reduction on the difference in QALYs between VenG and GClb, leading to a decrease in NMB by nearly [redacted] compared to the company's base case findings. In this case, the revised NMB was found to be [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively.

Table 53: Results for the del(17p)/TP53 mutation population when ERG's amendments are implemented one at a time (at list prices).

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Company's preferred base-case							
Ibrutinib	[redacted]	4.153				[redacted]	[redacted]
VenG	[redacted]	3.991	[redacted]	-0.163	[redacted]		
Results based on ERG's change in utility value for 'pre-progression, off treatment' status only							

Ibrutinib	[redacted]	4.153				[redacted]	[redacted]
VenG	[redacted]	3.802	[redacted]	-0.351	[redacted]		
Results based on ERG's change in time-to-event parameters and extrapolations only							
Ibrutinib	[redacted]	3.690				[redacted]	[redacted]
VenG	[redacted]	3.451	[redacted]	-0.238	[redacted]		
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab; NMB: net monetary benefit; WTP: willingness to pay. *This ICER falls within the south west quadrant of a cost-effectiveness plane, denoting cost savings per QALY forgone.							

Implementing the ERG's suggested base-case analysis—that is, carrying out all ERG amendments simultaneously—resulted in reductions in incremental costs (cost savings) and QALYs compared to the company's base-case values, leading to an overall reduction in NMB by approximately [redacted]. The resulting ERG's base-case NMB in the del(17p)/TP53 mutation population were [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY, respectively (Table 54). The ICER for this comparison falls within the south west quadrant of the cost-effectiveness plane reflecting cost savings per QALY forgone. The ICER resulting from the ERG base-case was [redacted] per QALY, as opposed to the company's base-case ICER at [redacted] per additional QALY.

Table 54: ERG's base case results for the del(17p)/TP53 mutation population (at list prices)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Company's preferred base-case							
Ibrutinib	[redacted]	4.153				[redacted]	[redacted]
VenG	[redacted]	3.991	[redacted]	-0.163	[redacted]		
ERG's preferred base-case							
Ibrutinib	[redacted]	3.690				[redacted]	[redacted]
VenG	[redacted]	3.326	[redacted]	-0.363	[redacted]		
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab; NMB: net monetary benefit; WTP: willingness to pay. *This ICER falls within the south west quadrant of a cost-effectiveness plane, denoting cost savings per QALY forgone.							

5.5.2 Additional sensitivity analyses carried out by the ERG.

Results of the additional sensitivity analyses run by the ERG can be seen below. A description of the analysis is given in Section 5.3.2. Briefly, the analysis involved: (i) using an alternative utility value for 'progression-free, off treatment' status (Scenario 1 in Table 55) and (ii) carrying out

the ERG's preferred amendments in TTE parameters but keeping the OS for VenG as per the company's specifications (Scenario 2 in Table 55). Under either scenario, findings agreed in direction with the results of the company's and the ERG's base-case analyses.

Table 55: Additional analyses carried out by the ERG.

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Scenario 1: alternative utility value for 'progression-free, off treatment' status (non-del(17p)/TP53 mutation population)							
GClb	[redacted]	6.610				[redacted]	[redacted]
VenG	[redacted]	7.443	[redacted]	0.833	[redacted]		
Scenario 1: alternative utility value for 'progression-free, off treatment' status (del(17p)/TP53 mutation population)							
Ibrutinib	[redacted]	4.153				[redacted]	[redacted]
VenG	[redacted]	3.814	[redacted]	-0.339	[redacted]		
Scenario 2: No change in OS for VenG (non-del(17p)/TP53 mutation population)							
GClb	[redacted]	5.692				[redacted]	[redacted]
VenG	[redacted]	7.232	[redacted]	1.541	[redacted]		

Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab; NMB: net monetary benefit WTP: willingness to pay.
*This ICER falls within the south west quadrant of a cost-effectiveness plane, denoting cost savings per QALY forgone.

6 End of life

The CS does not comment on the NICE end of life criteria in relation to VenG. The ERG considers this appropriate as the untreated CLL population would not normally have a life expectancy of less than 24 months when starting treatment with VenG.

7 Innovation

The CS considers that the innovative potential of VenG is demonstrated with the evidence from the CLL14 trial. The company cites the efficacy across all trial subgroups and the manageable adverse event profile along with high rates of undetectable MRD. In addition, the CS says that VenG provides a greater range of treatment options for the unfit CLL population, that VenG avoids the need for chemo-immunotherapy and that because of the fixed treatment duration VenG enables many patients to experience time without therapy. The CS states that this reduces the overall cost burden of treatment in this patient group. The ERG's clinical expert agrees that VenG is innovative, as targeted therapy avoiding traditional chemotherapy has not previously been considered for first-line treatment.

8 Overall conclusions

8.1 Clinical effectiveness evidence

Although there is good quality evidence for the effectiveness of VenG compared with GClb, the ERG has concerns regarding the maturity of the data and the generalisability to the UK population. The comparison of VenG to ibrutinib in the subgroup of people with del(17p)/TP53 mutation is associated with a high level of uncertainty meaning no conclusion of superiority can be made.

8.2 Cost-effectiveness evidence

The economic analysis carried out by the company is, on the whole, appropriate. Given the existing state of evidence, VenG appears to be a cost-effective option at conventional WTP thresholds in both the non-del(17p)/TP53 and del(17p)/TP53 mutation populations. However, immaturity of key effectiveness data (in VenG vs. GClb) and reliance on an unadjusted naïve

indirect comparison (for VenG vs ibrutinib) inevitably affect the cost-effectiveness calculations and introduce a layer of uncertainty in the overall results.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Wednesday 29 April 2020** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please note that you are not expected to submit additional evidence on the technology at this stage. Submission of any additional evidence requires prior agreement from NICE.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, first paragraph states: "*The CS presents evidence from one multi-centre randomised controlled trial (RCT) investigating the effectiveness and safety of VenG in people with untreated CLL who were unsuitable for treatment with fludarabine, cyclophosphamide and rituximab or bendamustine and rituximab (FCR/BR). The comparator in the CLL14 trial was chlorambucil and obinutuzumab (GClb). Unsuitability for FCR/BR was defined as the presence of coexisting conditions and a total cumulative illness rating scale (CIRS) of >6 or creatinine clearance <70ml/min"*	Please amend to: "*The CS presents evidence from one multi-centre randomised controlled trial (RCT) investigating the effectiveness and safety of VenG in people with* ***previously*** *untreated CLL* ***and coexisting medical conditions, which in the UK NHS context would typically mean patients*** *who were unsuitable for treatment with fludarabine, cyclophosphamide and rituximab or bendamustine and rituximab (FCR/BR). The comparator in the CLL14 trial was chlorambucil and obinutuzumab (GClb).* ***The presence of multiple coexisting medical conditions was defined by a cumulative illness rating scale (CIRS) of >6. In addition, glomerular filtration rate is an acceptable surrogate for decline in functional organ reserve, and therefore a threshold of CrCl < 70 mL/min was applied for inclusion in this study (for patients who did not meet the CIRS inclusion criterion).***	This statement is factually inaccurate and potentially misleading. The CLL14 trial inclusion and exclusion criteria have no mention of FCR/BR suitability.	Amended as follows to avoid mention of unsuitability for treatment in terms of trial eligibility. Unsuitability for treatment with FCR/BR treatment in the UK NHS context is discussed elsewhere. "The CS presents evidence from one multi-centre randomised controlled trial (RCT) investigating the effectiveness and safety of VenG in people with previously untreated CLL with co-existing medical conditions. The comparator in the CLL14 trial was chlorambucil and obinutuzumab (GClb). Presence of coexisting conditions was defined by a total cumulative illness rating scale (CIRS) of >6 or creatinine clearance <70ml/min"

Issue 2 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 states: *Time to the next anti-leukemic treatment (TTNT) defined as the time between the date of randomisation and the date of a*	Please amend to: Time to the next anti-leukemic treatment (TTNT) defined as the time between the date of randomisation and the date of a patient receiving a second line therapy **or death** also	The current statement is incorrect.	Amended as proposed.

patient receiving a second line therapy also suggested that VenG has a significantly lower hazard rate of next treatment or death than GClb (stratified hazard ratio 0.51 (95% CI 0.34 to 0.7897, p = [redacted]))	suggested that VenG has a significantly lower hazard rate of next treatment or death than GClb (stratified hazard ratio 0.51 (95% CI 0.34 to **0.78**, p = [redacted]))		

Issue 3 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 states: *"The CS presents minimal residual disease (MRD) as a secondary trial outcome, although this was not a NICE scoped comparator"* The use of the word *"comparator"* is incorrect and should instead refer to an *"outcome"*.	Please amend to: *"The CS presents minimal residual disease (MRD) as a secondary trial outcome, although this was not a NICE scoped **outcome**"*	The current statement is incorrect.	Typographical error corrected.

Issue 4 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 states: *'The company reports that VenG achieved 75.5% MRD negativity compared to 35.2% in the GClb arm 3 months after treatment completion, but this reduced to 47.2% and 7.4%, respectively, 18 months after treatment completion.'*	Please amend to: *'The company reports that VenG achieved 75.5% MRD negativity compared to 35.2% in the GClb arm 3 months after treatment completion or **early termination**, but this reduced to 47.2% and 7.4%, respectively, 18 months after treatment completion.'*	The current statement is incorrect.	This is the Summary and it is defined in full in ERG section 4.4.6, but amended for clarity.

Issue 5 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 states: 'The majority of participants experienced at least one treatment-emergent adverse event (TEAE); 14.6% and 15.9% of the VenG and GClb groups, respectively, discontinued a treatment for TEAEs.'	Please amend to: 'The majority of participants experienced at least one treatment-emergent adverse event (TEAE); **17.0%** and **16.4%** of the VenG and GClb groups, respectively, discontinued a treatment for TEAEs.'	To align with figures in updated Clinical Study Report	No change, not a factual error (data were not provided in the company submissions)

Issue 6 Summary of clinical effectiveness evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 states: *Tumour Lysis Syndrome (TLS) was reported in three VenG treated participants and in five GClb treated participants*	Please amend to: *Tumour Lysis Syndrome (TLS) was reported in three VenG treated participants and in five GClb treated participants.* ***All AEs in the VenG arm occurred prior to the first dose of venetoclax***	Could be misleading as TLS occurred before treatment.	No change, not a factual error.

Issue 7 Summary of ERG's critique of clinical effectiveness evidence submitted

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 of the ERG Report states: *"The ERG also notes that the analyses of DOR, TTNT and event-free survival were performed without an assessment of proportional hazards."* Page 47 of the ERG Report also states, in relation to TTNT:	The statement on Page 15 should be amended as follows: "*The ERG also notes that the analyses of DOR and event-free survival were performed without an assessment of proportional hazards. The assumption of proportional hazards for TTNT was assessed within the cost-effectiveness analysis, with the conclusion that the assumption could not be accepted.*	The current statement is incorrect.	We have updated the text on page 15 by removing TTNT from the listed outcomes. We have updated the text on page 47 to clarify our statement

"There is no assessment of proportional hazards" These statements are incorrect. The proportional hazards assessment of TTNT is discussed in the CS Document B, Page 94 and presented fully in Appendix M, Pages 251–253. This is then further addressed in the Addendum on Page 36, where it is stated that *"the conclusions on proportionality of hazards remain the same (please refer to Section B.3.3.3 of the original submission document)"* as compared with the original submission.	The statement on Page 47 should be amended as follows: *"An assessment of proportional hazards was conducted on the August 2018 data cut, concluding that the assumption could not be accepted"*		

Issue 8 Summary of ERG's critique of clinical effectiveness evidence submitted

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 states: *"The analysis for OS was presented without a discussion of proportional hazards in the clinical effectiveness section but in the cost-effectiveness section of the CS the assumption of proportional hazards was made"* This statement currently incorrectly implies that the proportional hazards assumption for OS was simply stated in the cost-effectiveness section of CS Document B, without further explanation, however full details	Please amend to: *"The analysis for OS was presented without a discussion of proportional hazards in the clinical effectiveness section but this was discussed fully in the cost-effectiveness section of the CS and the assumption of proportional hazards was made"*	The current statement incorrectly implies a factual inaccuracy and does not accurately reflect the content provided in the CS.	We have clarified the text on page 15.

on the analysis that led to this conclusion were provided.			

Issue 9 Summary of cost effectiveness submitted evidence by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 states: *"Time-to-next treatment (TTNT) was extrapolated using an independent (Weibull) model applied to CLL14 data for both VenG and GClb arms."*	Please amend to: *"Time-to-next treatment (TTNT) was extrapolated using an independent (**Loglogistic**) model applied to CLL14 data for both VenG and GClb arms."*	This was updated from Weibull to loglogistic in the addendum submission	We have corrected the text on page 17.

Issue 10 Summary of cost effectiveness submitted evidence by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22, final sentence states: ….. "*The ICER resulting from the ERG base-case was* [redacted] *per QALY, as opposed to the company's base-case ICER at* [redacted] *per QALY"*	Please delete	This sentence risks being misinterpreted as the ICERs are south west quadrant ICERs, which are not interpreted in the same way as conventional ICERs. NMB values are already presented in the sentence above and should suffice	The ERG agrees with this suggestion. The sentence in question has been deleted.

Issue 11 Critique of company's decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 states: "*The anticipated marketing authorisation is: Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. Committee for Medicinal Products for Human Use (CHMP) positive opinion was granted in January 2020, and marketing authorisation in this indication is expected in April 2020*".	Please amend to: "*The ~~anticipated~~ marketing authorisation is: Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. Committee for Medicinal Products for Human Use (CHMP) positive opinion was granted in January 2020, and marketing authorisation in this indication ~~is expected in April 2020~~* ***was granted in March 2020***	VenG has now received marketing authorisation	Statement correct at time of writing. Amended as proposed.

Issue 12 Critique of trials of the technology of interest, their analyses and interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38, Table 3: The values for *IGHV mutational status, mutated* for the full population are misreported for VenG and GClb.	These values should read as follows: VenG arm 35.2%, GClb arm 38.4 % The values are currently swapped in the table	The current results are incorrectly reported.	Amended.

Issue 13 Summary and critique of company approach to statistical analysis and results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 states:	Please amend to:	The interim analysis was planned for when 65% of planned PFS	No change. This is not a factual error. The statement is

Instead, the analyses used the data from the planned interim analysis which was conducted when 65% of the planned PFS events (n=107) had occurred. The interim analysis was originally planned for when 75% of PFS events (n=128) had occurred. The change was based on recommendations from the trial's independent data monitoring committee though a protocol amendment (version 7) which describes why the interim analysis was performed earlier than originally planned. Hence, these data are very immature and it is not possible to draw conclusions for all of the specified outcomes	*Instead, the analyses used the data from the planned interim analysis which was conducted when 65% of the planned PFS events (**n=110**) had occurred. The interim analysis was originally planned for when 75% of PFS events (n=128) had occurred. The change was based on recommendations from the trial's independent data monitoring committee though a protocol amendment (version 7) which describes why the interim analysis was performed earlier than originally planned. ~~Hence, these data are very immature and it is not possible to draw conclusions for all of the specified outcomes.~~* **Based on the outcomes from the interim analysis, positive outcomes have been observed for majority of the efficacy endpoints except OS, which needs longer follow-up for maturity.**	events had occurred. The equates to n=110. At the predicted cut-off date of 17 Aug 2018, 107 PFS events had occurred. The statement on data immaturity is broad and should instead relate specifically to OS	maintained to support the following sentence which refers to extrapolations.

Issue 14 Summary of trial results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44 Table 4 Table references the FDA report, there is a discrepancy between the FDA and CSR for the PFS at 2 and 3 year. We consider it more appropriate to reference the updated CSR.	<table><tr><td>Outcome (95% CI)</td><td>VenG (n=216)</td><td>GClb (n=216)</td></tr><tr><td colspan="3">Primary outcome: Investigator Assessed PFS (August 2019 data-cut)</td></tr><tr><td>1 year PFS 2 year PFS 3 year PFS Median PFS</td><td>[redacted] 88.17 (83.72, 92.61)[a]</td><td>[redacted] 64.58 (57.95, 71.20)[a]</td></tr></table>	We consider it more appropriate to reference the updated CSR.	2 year PFS reported in ERG Table 4 aligns with that reported in CS addendum Table 4 with rounding (88.2% vs 64.1%) as well as the FDA document. The value for GClb reported in the proposed amendment and the CSR supplement (64.58%) does not align with that reported in CS addendum Table 4 (64.1%). The ERG has corrected the company's error.

		81.88 (76.50, 87.23) Not reached	49.51 (42.41, 56.60) 35.6 ([redacted])		3 year PFS reported in ERG Table 4 is exactly as reported in CS addendum Table 4 (the ERG obtained 95% CI from CSR supplement). There is a discrepancy between the upper CI reported in the proposed amendment for VenG (87.23) and that reported in the CSR addendum (87.26). No change.
	Please update the table as follows and reference CSR supplement:				

Issue 15 Patient reported outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49, states: "*Whilst it is difficult to conclude what may be influencing this [redacted] result.* [redacted]	Please amend to: "~~*Whilst*~~ *It is difficult to conclude what may be influencing this [redacted] result.* [redacted]	This sentence is potentially misleading and is factually inaccurate. VenG patients are only on treatment for a year, whereas the progression free period is much longer. Another explanation for the similar PROs could be because this is an elderly and co-morbid population that has co-morbidities that may have a larger bearing on their perception of quality of life.	This is not a factual error.

Issue 16 Critique of trials identified and included in the indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG Report states: *"However, the company did not update the indirect comparisons with ibrutinib using the corrected data. The comparisons between the ibrutinib studies and CLL14 presented below are therefore based on the original (incorrect) baselines and results provided in the CS. Updated results for PFS and OS are also presented in* ***Error! Reference source not found.*** *below"* This statement is incorrect. Updated PFS and OS naïve indirect comparisons using data from the August 2019 data cut were included in addendum. An updated feasibility assessment was not provided in the addendum; however this was due to the small change in population numbers and the conclusions remained the same as those presented in the original submission.	Please amend to: *"The company did not provide an updated feasibility assessment for the indirect comparisons with ibrutinib using the corrected data as the conclusions remained the same between the original submission and the addendum. The comparisons between the ibrutinib studies and CLL14 presented below are therefore based on the original (incorrect) baselines. Updated results for PFS and OS were provided in the CS Addendum and are also presented in Table 7 below"*	The current statement is incorrect and does not accurately reflect the content provided in the CS.	The ERGs statement referred to the first set of clarification responses provided by the company and was not updated in light of the CS addendum and addendum clarification responses. Text deleted, and added 'these are presented in Table 6 below' to previous sentence.

Issue 17 Critique of trials identified and included in the indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 56 Table 6 In the CLL14 column the del(17p) is quoted as not reported. This can be found on page 26 of the CSR supplement. ***del(17p)/TP53 mutation: 25*** *del(17p): not reported* *TP53 mutation: 23*	Please amend table as follows: ***del(17p)/TP53 mutation: 25*** *del(17p):* ***17*** *TP53 mutation: 23*	This is factually incorrect	These data were not reported in the CS and could not be located in the CSR supplement without signposting. CSR p26 checked and table amended.

Issue 18 Serious adverse events and deaths

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61, Table 11 list *Myocardial infarction*	Please amend to: ***Acute*** *Myocardal Infarction*	The current statement is incorrect.	Reported exactly as presented in CS Table 30. Not a factual error, no change.

Issue 19 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 77 and 117 of the ERG Report describes the two populations considered in the cost-effectiveness analysis: • *"Patients with previously untreated CLL, without del(17p)/TP53 mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR.*	The population descriptions on both pages should be amended as follows: • *"Patients with previously untreated CLL, without del(17p)/TP53 mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR.* • *Patients with previously untreated CLL, with del(17p)/TP53 mutation."*	The current statement is incorrect.	The ERG agrees with this suggestion. The suggested change has been made on both pages.

• *Patients with previously untreated CLL, with del(17p)/TP53 mutation, with known comorbidities that make them unsuitable for treatment with FCR/BR."* The second population described is incorrect. The suitability for treatment with FCR/BR is not relevant for the patient population with del(17p)/*TP53* mutation as FCR/BR are not licensed or approved for this population.			

Issue 20 Non-del(17p)/TP53 mutation population: progression-free survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 states : The progression free survival extrapolation methods are being discussed for the non-del(17p)/TP53 mutation population, the ERG mentions that *"This meant that the effect of the del(17p)/TP53 mutation was modelled separately for both arms".* We suggest amendment to this sentence as it does not hold true for OS since we use a dependent model there, but it does hold true for PFS.	Please amend to: *"the effect of the del(17p)/TP53 mutation was modelled separately for both arms* ***for the PFS extrapolations****"*	The statement is misleading and eludes to the fact that the method was applied to all outcomes (i.e., OS as well) which is factually not correct.	Not a factual error. This is clearly under the title of section 5.2.6.1: Non-del(17p)/TP53 mutation population: progression-free survival

Issue 21 Non-del(17p)/TP53 mutation: Time-to-next treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 89 Section 5.2.6.2: End of the 2nd paragraph on the page states: *"Recall that the company treated death events as TTNT events, which may confound the extrapolations."*	Please amend to: *"In the IPD analysis, death was treated as a censoring event in the TTNT curves"*	The statement is incorrect since death events are not treated as TTNT events in any of the analyses. There is probably some confusion as for the TTNT analyses, death is indeed treated as an event.	It is unclear what the company's request is. Table 21 of the original company submission and Table 6 of the company addendum both support the ERG text. This is not a factual error.

Issue 22 Non-del(17p)/TP53 mutation: Time-to-next treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90, Section 5.2.6.2, 5th paragraph under 'Extrapolations' *"Secondly, the constraint of the hazard rate for TTNT to not fall below background mortality is necessary and comes into effect at just before 6 years for the VenG Weibull extrapolation and at 13 years for the GClb extrapolation."*	If a log-logistic distribution is being used for VenG and GClb TTNT curves then the description should be the following: *"Secondly, the constraint of the hazard rate for TTNT when **using a log-logistic distribution** to not fall below background mortality is necessary and comes into effect just before 6 years for the VenG extrapolation and **just before 14 years** for the GClb extrapolation."*	Using a Weibull distribution we were unable to replicate the values. Therefore assume results are factually incorrect.	We have updated the text.

Issue 23 Non-del(17p)/TP53 mutation: Time-to-next treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.2, Page 90, 6th paragraph under 'Extrapolations'	If a log-logistic distribution is being used for VenG and GClb TTNT curves then the description should be the following:	Using a Weibull distribution we were unable to replicate the values. Therefore assume results are	We have updated the text to reflect that we were referring to

*"Whilst the ERG interprets the resulting estimates for GClb to be plausible, the predictions for VenG remain constrained by background mortality within the **first 7 years** of the economic model."*	*"Whilst the ERG interprets the resulting estimates for GClb to be plausible, the predictions for VenG **using a log-logistic distribution** remain constrained by background mortality **6.4 years** of the economic model."*	factually incorrect. We were able to get values close to within first 7 years using the log-logistic distribution which is what has been described.	the spline models mentioned in the previous sentence.

Issue 24 Non-del(17p)/TP53 mutation: Time-to-next treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 92, Section 5.2.6.3, Table 26 reports: ERG TTNT landmark estimates for VenG 5year: [redacted] 10 year: [redacted] 20 year: [redacted]	The values should be: ERG TTNT landmark estimates for VenG 5 year = [redacted] 10 year = [redacted] 20 year = [redacted]	Using the ERG model provided for the non-del17p population, we were unable to replicate these landmark values for TTNT in the VenG arm.	The ERG have updated the table with the correct values.

Issue 25 Non-del(17p)/TP53 mutation: Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 27, Page 93-94 It is unclear if numbers in table 27 refer to the company or ERG digitisation. If table 27 does in fact refer to the company model please change as proposed.	Background mortality: 5 year [redacted]; 10 year [redacted]; 20 year [redacted] CLL OS 3 year - [redacted]	The numbers do not reflect the figures in the company model	We have amended the values queried by the company.

Issue 26 Del(17p)/TP53 mutation population: VenG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.6.5, Page 95, 1st paragraph *"The company appeared to include patients who received GClb in their analysis, despite these patients being irrelevant and potentially misleading for the eventual comparison to ibrutinib"*	The statement should be omitted	The statement is misleading since, although GClb patients are used as an anchor point to determine the covariate for the treatment effect for VenG, GClb patients are not included in the actual analyses for VenG versus ibrutinib.	This is not a factual error.

Issue 27 Critique of trials of the technology of interest, their analyses and interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97 *"There was no clear evidence of violation of proportionality for PFS or OS, though the small sample size of the del(17p)/TP53 mutation group makes it difficult for the ERG to be confident that proportionality is a reasonable assumption to make."*	Please amend to: *"~~There was no clear evidence of violation of proportionality for PFS or OS, though~~ The small sample size of the del(17p)/TP53 mutation group makes it difficult for the ERG to be confident that proportionality is a reasonable assumption to make."*	On page 39 of the addendum submission evidence is provided to support the violation of the proportional hazard's assumption	Not a factual error. The present evidence is inconclusive.

Issue 28 ERG's base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102, Section 5.2.6.6, Table 30 and page 128, Section 5.3.1, Table 50	The ERG base case description for the OS model should be: *Dependent 1-knot hazard spline extrapolation of CLL14 data and hazard ratio for ibrutinib*	The ERG model provided for the del17p population uses this modelling method and Table 28 also states that a dependent model was used for OS.	We have amended the text in Table 30 and Table 50.

ERG Base Case for del17p/TP53 mutation OS = Independent 1-knot hazard spline extrapolation of CLL14 data and hazard ratio for ibrutinib		The ERG results also match with the dependent model OS option.	

Issue 29 Del (17p)/TP53mutation population: ibrutinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102 states *"The ERG also preferred to use the 1 knot dependent spline model for VenG TTNT as this predicted that later lines of therapy would be taken for [redacted] years, rather than [redacted] years as under the company's assumptions."* It later states *"In both ERG and company base-cases, the average time on later lines of therapy was [redacted] years. "*	Please amend to: *"The ERG also preferred to use the 1 knot **hazard** dependent spline model for VenG TTNT as this predicted that later lines of therapy would be taken for [redacted] years, rather than [redacted] years as under the company's **base case**."* Please amend to: *"In both ERG and company base-cases, the average time on later lines of therapy was [redacted] years."*	This is factually incorrect The value correct value for VenG is 0.65 which has been incorrectly rounded to 0.07	We have updated the text with corrections and clarification.

Issue 30 Disutility due to adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 108, Table 34, describes the disutility values and QALY decrements applied due to adverse events. The following data points are reported incorrectly: *"Diarrhoea Disutility SE; 0.005*	These data values should be corrected to the following values: *"Diarrhoea Disutility SE; 0.008* *Dyspnoea Duration SE; 2.10* *Neutropenia Disutility SE: 0.009*	The current values are incorrect and do not align with the CS.	The values in Table 34 of the ERG report are consistent with those utilised in the company's decision model. The company's base case cost-effectiveness results have been calculated on

Dyspnoea Duration SE; 1.27 *Neutropenia Disutility SE: 0.002* *Pneumonia Disutility SE; 0.004* *Sepsis Disutility SE; 0.004"*	*Pneumonia Disutility SE; 0.020* *Sepsis Disutility SE; 0.020"*		the basis of these values. No amendments have been made.

Issue 31 Routine care and monitoring costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 38, Page 112 describes the pre- and post-progression resource use frequencies used in the model. This includes a row for *"platelet infusion"* This is incorrect. Resource use for "platelet infusion" is not presented in the equivalent table of the CS Document B (Table 52, Page 123) and is not included in AbbVie's cost-effectiveness model.	The row for *"platelet infusion"* in Table 38, Page 112 should be removed.	The current table is incorrect.	The ERG agree. The suggested change has been made.

Issue 32 Additional sensitivity analyses carried out by ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 135, Section 5.5.2, Table 55 reports: *Scenario 1: alternative utility value for 'progression-free, off treatment' status (non-del(17p)/TP53 mutation population)* *ICER (£/QALY) =* [redacted] *NMB (WTP: £20k per QALY) =* [redacted] *NMB (WTP: £30k per QALY) =* [redacted]	The values should be: NMB (WTP: £20k per QALY) = [redacted] NMB (WTP: £30k per QALY) = [redacted] and	We were able to replicate the Incremental cost and incremental QALY outcomes. However, the ICER and the NMBs generated from these incremental costs and QALYs are incorrect and should be updated.	The small discrepancies between the results calculated by the ERG and those calculated by the company are due to the fact that the ERG's calculations use a more precise value for the alternative utility estimate (0.773457027, rather the rounded-up number of 0.7735 given in the ERG report and used by the company). The rounded number has been

Scenario 1: alternative utility value for 'progression-free, off treatment' status (del(17p)/TP53 mutation population) *ICER (£/QALY) =* [redacted] *NMB (WTP: £20k per QALY) =* [redacted] *NMB (WTP: £30k per QALY) =* [redacted]	*ICER (£/QALY) =* [redacted] *NMB (WTP: £20k per QALY) =* [redacted] *NMB (WTP: £30k per QALY) =* [redacted]		replaced by the full, 8-decimal place number in the ERG report. Using this number, the company should be able to generate results that agree with those in the ERG report. There are typographical errors Section 5.5.2, Table 55, as the NMB values at the £20k and £30k WTP thresholds should be reversed. The necessary corrections has been made in Section 5.5.2, Table 55.

The following section includes inaccuracies in the confidential marking in the ERG report

Issue 33 Summary of clinical effectiveness submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 &12 The CS addendum and CSR supplement: data cut August 2019 ([redacted] months median follow-up)	Remove yellow highlighting The CS addendum and CSR supplement: data cut August 2019 (39.6 months median follow-up)	This is available in the public domain	39.6 months is marked by the company as AIC in the CS addendum. The ERG has corrected the company's error.

Issue 34 Summary of exploratory and sensitivity analyses undertaken by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22 of the ERG Report presents data from the additional ERG cost-effectiveness analyses.	Add blue CIC highlighting to the statement *"VenG was* [redacted] *against GClb"*	This relates to confidential results of cost-effectiveness analyses based on the list price of VenG.	The suggested change has been made.

The overall results are incorrectly missing CIC highlighting.			

Issue 35 Critique of trials of the technology of interest, their analyses and interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3, Page 38 of the ERG Report presents the key baseline characteristics from the CLL14 trial. The value for the proportion of patients with mutated TP53 in the GClb arm of the ITT population has been underlined, but not highlighted yellow.	Add yellow highlighting to the value "[redacted]" in Table 3, Page 38 (row: TP53 mutation status, mutated, n/N [%]; column: Full study population, GClb)	These are unpublished data from the CLL14 trial. Publication date is not yet determined but it is anticipated that the information will be in the public domain by end of 2021.	Missing highlight added.

Issue 36 Critique of trials identified and included in the indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG Report presents baseline characteristic data from the CLL14 trial. The median age of the ITT population is incorrectly marked as AIC.	Remove the yellow AIC highlighting from *"the median age of the CLL14 whole trial population was 72 years"*	NICE guidelines state that ACIC marking should be kept to a minimum. This value is not confidential.	Data obtained from the CSR and not in the public domain, but marking removed as requested.

Issue 37 Overview of treatment emergent adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 of the ERG Report presents the proportion of patients experiencing TEAEs in each treatment arm. These percentages have been correctly highlighted	Add underlining to the figures in the statement *"TEAEs were experienced in [redacted]% of participants in the VenG arm and [redacted]% of participants in the GClb arm"*	These are unpublished data from the CLL14 trial. Publication date is not yet determined but it is anticipated that the information will be in the public domain by end of 2021.	Missing underlines added.

yellow but have not been underlined.			

We have also provided the following typographical errors for completeness.

Issue 38 Summary of clinical effectiveness submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 states: *"A naïve indirect comparison was made between CLI14 and three separate studies to compare VenG with ibrutinib for people with previously untreated CLL and del(17p)/TP53 mutation."*	Proposed amend: *"A naïve indirect comparison was made between **CLL14** and three separate studies to compare VenG with ibrutinib for people with previously untreated CLL and del(17p)/TP53 mutation."*	This is a typographical error.	Typographical error corrected.

Issue 39 ERG commentary on the robustness if evidence submitted by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 contains a typographic error when describing the strengths of the trial: *"Where available, key evidence on treatment effectiveness was drawn from the CLL14."* The same error appears on Page 68 of the ERG Report when describing the generalisability of the trial:	The bullet point on Page 21 should be corrected to: *"Where available, key evidence on treatment effectiveness was drawn from the CLL14 **trial**."* The statement on Page 68 should be corrected to: *"The ERG noted concerns regarding the generalisability of the CLL14 **trial** to the UK population."*	This is a typographical error.	Typographical error corrected.

"The ERG noted concerns regarding the generalisability of the CLL14 to the UK population."			

Issue 40 Summary and critique of company approach to statistical analysis and results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 of the ERG Report contains a typographical error: *"The change was based on recommendations from the trial's independent data monitoring committee though a protocol amendment (version 7) which describes why the interim analysis was performed earlier than originally planned."*	This sentence should be corrected to: *"The change was based on recommendations from the trial's independent data monitoring committee **through** a protocol amendment (version 7) which describes why the interim analysis was performed earlier than originally planned."*	This is a typographical error.	We have corrected this typographical error.

Issue 41 Correction of Del(17p)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG Report misspells *"del(17p)"* on the following pages: Page 49 as *"del(17pdel)"* and *"17p(del)"* Page 52 as *"(del)17p"* Pages 64 and 101 as *"del17p"* Page 124 as *"del(17)"*	These should be corrected to *"del(17p)"*	This is a typographical error.	Typographical errors corrected.

Issue 42 Critique of trials identified and included in the indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG Report misspells *"Kaplan-Meier"* in the footnote of Table 7, Page 56 as *"Kapan-Meier"*	*"Kapan-Meier"* should be corrected to *"Kaplan–Meier"*	This is a typographical error.	We have corrected this typographical error.

Issue 43 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG Report misspells *"chlorambucil"* as *"chrolambucil"* in Table 8, Page 58	*"Chrolambucil"* should be corrected to *"chlorambucil"*	This is a typographical error.	Typographical error corrected.

Issue 44 Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 78 contains a formatting error. A page break has been captured inside the caption for Table 22 causing a page break to appear on Page 78 within the cross-reference to Table 22.	The caption and cross-reference to Table 22 should be updated to remove the page break.	This is a typographical formatting error.	The identified formatting error has been rectified.

Issue 45 Interventions and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80 contains a typographical error: *"Using the CSR categorisation in the model resulted in a small difference cost-effectiveness*	This sentence should be corrected to: *"Using the CSR categorisation in the model resulted in a small difference **in the** cost-*	This is a typographical error.	This typographical error has been corrected.

results for VenG against its comparators"	*effectiveness results for VenG against its comparators"*		

Issue 46 Interventions and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80 of the ERG Report contains a typographical error, with a repeated word: *"the corresponding populations are described below in* ***Error! Reference source not found.*** *below"*	This sentence should be corrected to remove one of the incidences of *"below"*	This is a typographical error.	This typographical error has been corrected.

Issue 47 Miscellaneous costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117 of the ERG Report contains a typographical error: *"Costs associated with terminal care were calculated and included in the model in the same was as in NICE appraisal TA561"*	This sentence should be corrected to: *"Costs associated with terminal care were calculated and included in the model in the same* ***way*** *as in NICE appraisal TA561"*	This is a typographical error.	This typographical error has been corrected.

Issue 48 Probabilistic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 119 of the ERG Report contains a typographical error: *"Probabilistic sensitivity analysis (PSA) were carried out…"*	This sentence should be corrected to: *"Probabilistic sensitivity* ***analyses*** *(PSA) were carried out…"*	This is a typographical error.	This typographical error has been corrected.

Issue 49 Innovation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 136 of the ERG Report contains a typographical error: *"VenG enables many patients experience time without therapy"*	This sentence should be corrected to: *"VenG enables many patients **to** experience time without therapy"*	This is a typographical error.	This typographical error has been corrected.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Venetoclax with obinutuzumab for treating untreated chronic lymphocytic leukaemia

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

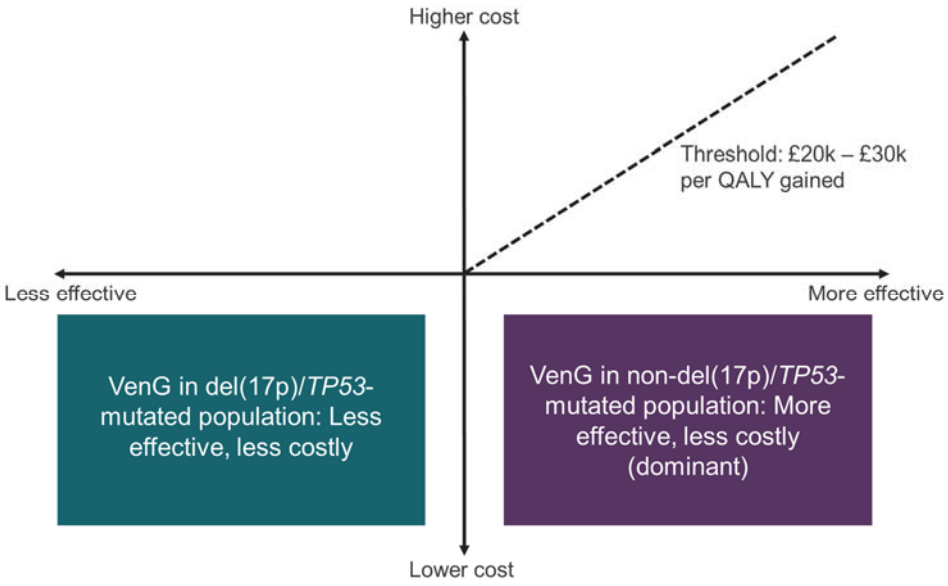
- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: June 2020

1. Summary of the technical report

1.1 Venetoclax with obinutuzumab (VenG) falls in the south east quadrant of the cost-effectiveness plane compared with obinutuzumab with chlorambucil (GClb) in the non-del(17p)/*TP53*-mutated population, indicating it is dominant (less costly and more effective). In the del(17p)/*TP53*-mutated population VenG falls in the south west quadrant compared with ibrutinib, indicating it is less effective and less costly.



For the non-del(17p)/*TP53*-mutated population in the economic model, venetoclax and chlorambucil are administered over a fixed treatment duration of 12 cycles, while obinutuzumab is administered over a fixed treatment duration of 6 cycles.

[redacted].

The costs of subsequent second-line anti-leukemic therapy are also considered in the model, with 3 key inputs: 1) the type of treatment mix received; 2) the timepoint at which patients start receiving second-line therapy, and 3) how long patients stay on second-line therapy. Based on clinical expert input, the company assumed second-line treatment to be either ibrutinib, or venetoclax in combination with rituximab (VenR). Literature indicates a median treatment duration of 39 months for ibrutinib,

and 24.4 months for VenR; both options have a high acquisition cost per cycle. The proportion of patients receiving second-line treatment is modelled by subtracting the time-to-next-treatment (TTNT) curve from the overall survival (OS) curve for VenG and GClb. No OS difference between treatment arms was observed in the company's CLL14 trial, and OS is modelled to be the same for both VenG and GClb. The risk of patients experiencing a TTNT event (i.e. starting a new treatment) was reduced in the VenG arm compared to the GClb arm in CLL14, and the curves are modelled differently.

[redacted]

compared to those receiving GClb,

[redacted] are accrued for GClb over the model horizon. This is the key driver of GClb having higher total costs and being dominated by VenG.

Illustrative comparison of proportion of patients moving onto second-line treatment over time

[redacted]

1.2 In summary, the technical team considered the following:

Issue 1 The company submission limits the positioning of VenG to the treatment of previously untreated fludarabine, cyclophosphamide and rituximab (FCR)- or bendamustine and

rituximab (BR)-unsuitable patients without del(17p)/*TP53* mutation, and the treatment of previously untreated patients with del(17p)/*TP53* mutation. This is narrower than the NICE scope and EMA marketing authorisation indication, which cover patients with previously untreated CLL regardless of mutation status or suitability to receive FCR or BR. Due to the restricted patient population, the company does not consider FCR or BR to be relevant comparators despite both being included in the NICE scope, and does not provide data for these comparisons.

Issue 2 The progression-free survival (PFS) projections for VenG and GClb are uncertain due to the immaturity of the data and clear differences between the extrapolation models tested by the company and the ERG. The ERG disagrees with the company's log-logistic model, as it overestimates 3-year PFS compared to all observed data sources and is reliant on the constraint that the hazard rate should not drop below background mortality. The ERG instead favours an independent 2-knot hazard spline model, as it predicts a 5-year PFS rate for GClb closest to the observed data from CLL11, and a 10-year PFS rate for VenG close to that estimated by the ERG's clinical expert.

Issue 3 There is considerable uncertainty associated with the OS extrapolations for VenG and GClb due to the immaturity of the CLL14 OS data. At the time of data cut off, [redacted] of all randomised patients in CLL14 had died. After consulting clinical and economic experts and analysing longer term data from CLL11, RESONATE and Warwick ERG's network meta-analysis (NMA) from TA561, the company considered that applying an exponential curve based on the GClb data to both treatment arms provided the most plausible OS extrapolation. The ERG considers none of the company's extrapolation models to be plausible, as they are all too reliant on the background mortality constraint. The ERG modelled the hazard rate from CLL14 for 3

years, before applying an alternative hazard rate based on the longer-term data from the ERIC trial after this point. The resulting extrapolation matches more closely with the 5-year GClb OS data from CLL11, as well as the estimates of the ERG's clinical expert.

Issue 4 In the company's model, subsequent treatment costs are applied from initiation of second-line treatment until death, and are not constrained by the average treatment durations reported in the literature. This approach may overestimate subsequent treatment costs. The difference between the OS and TTNT curves determines the proportion of patients receiving subsequent treatment, and the TTNT extrapolations are subject to a high degree of uncertainty. The company used an independent log-logistic model to extrapolate TTNT, as it provides estimates relatively close to the observed data from CL11 and aligns with the PFS curve chosen by the company. The ERG does not consider the company's extrapolation clinically plausible as it is reliant on the background mortality constraint. Instead, the ERG calculated a hazard ratio that could be applied to its preferred PFS curve to derive an extrapolation for TTNT. The ERG's curve is closer than that of the company to the observed data from CLL11, and is less reliant on the background mortality constraint.

Issue 5 The indirect comparison against ibrutinib in del(17p)/*TP53*-mutated patients is subject to considerable uncertainty. The small patient numbers and lack of prognostic patient characteristics reported for the trials identified in the systematic literature review (SLR) preclude a matching-adjusted indirect comparison (MAIC). As a result, the company conducted an unadjusted naive indirect comparison, which numerically favours ibrutinib with wide confidence intervals. The ERG considers this analysis to be inadequate, given the considerable heterogeneity

between the population of CLL14 and the studies identified by the SLR. In the absence of more robust data, the ERG incorporated the company's base-case PFS and OS hazard ratios for VenG versus ibrutinib derived from the indirect comparison into its cost-effectiveness model.

Issue 6 To derive the OS and PFS curves in the del(17p)/*TP53*-mutated population for the cost-effectiveness model, the company applied a covariate to the overall CLL14 trial data to model the impact of the mutation on efficacy outcomes. The company used the same extrapolation models as for the non-del(17p)/*TP53*-mutated population, applying the PFS and OS hazard ratios from the indirect comparison to derive the ibrutinib curves. The ERG considers the PFS and OS curves that result from this to be implausible, as in the resulting Markov traces patients spend almost no time in the post-progression state. The ERG identified a 1-knot hazard spline model to be more clinically plausible as it produces estimates closer to that of the ERG's clinical expert, and results in a more plausible post-progression duration than the company's model.

Issue 7 The utility values collected from CLL14 are unfeasibly high, exceeding those of the age-matched general population. As a result, the company used the utility values from TA343 in both treatment arms of the cost-effectiveness model, having been unable to identify any other relevant source of utility values specific to the UK population following an SLR. The ERG agrees with the company's rationale for not using the utilities from CLL14, but considers the value for the 'pre-progression off treatment' state taken by the company from TA343 to be implausible. The ERG derived an alternative gender-weighted, age-specific utility value from the general population using the methodology from TA343 that it considers more appropriate.

Issue 8 No evidence of significant [redacted] between the VenG and GClb treatment arms was reported across the 3 PRO tools used in CLL14: the EQ-5D-3L, MDASI-CLL and EORTC QLQ-C30. This is despite the fact that the PFS hazard ratio was 0.31 in favour of VenG in CLL14 in the non-del(17p)/*TP53*-mutated population. The ERG considers the lack of health-related quality of life benefit for VenG [redacted] given its PFS benefit, and [redacted]. There is a risk that applying the utility values from TA343 may overestimate the HRQoL impact of patients remaining progression-free on VenG. In a scenario in which the utilities from CLL14 are applied, the QALY difference between VenG and GClb is reduced substantially compared with the base case.

1.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence is immature. Median OS has not been met, and only [redacted] of 432 patients have died.
- No direct comparative evidence is available against ibrutinib in patients with del(17p)/*TP53* mutation. The indirect comparison is based on very small patient numbers, and is unadjusted for differences between study populations with considerable heterogeneity identified.

1.4 The company's base-case cost-effectiveness results use the list price for VenG and all comparators (GClb and ibrutinib). Comparator discounts are confidential. Results including all confidential discounts prepared by the ERG will be discussed by the committee.

1.5 Taking these aspects into account, the technical team agrees with the ERG's preferred assumptions, which result in VenG being dominant (both less costly and more effective) in patients without del(17p)/*TP53* mutation

unsuitable for FCR or BR. VenG has a net monetary benefit (NMB) of [redacted] at a willingness-to-pay (WTP) threshold of £20,000 per QALY, and a NMB of [redacted] at a WTP threshold of £30,000 per QALY compared with GClb in this patient population. In patients with del(17p)/*TP53* mutation, the ERG's preferred assumptions result in VenG being both less costly and less effective than ibrutinib. VenG has a NMB of [redacted] at a WTP threshold of £20,000 per QALY, and a NMB of [redacted] at a WTP threshold of £30,000 per QALY. These estimates do not include the commercial arrangements for venetoclax, obinutuzumab and ibrutinib, because these are confidential and cannot be reported here. Estimates that included these commercial arrangements would be lower than those reported above.

1.6 VenG does not meet the criteria to be considered a life-extending, end-of-life treatment when compared with either GClb or ibrutinib. The untreated CLL population would not normally have a life expectancy of less than 24 months when starting treatment with VenG.

1.7 In terms of innovation and unmet need, the company have stated that venetoclax is a first-in-class, oral, selective inhibitor of B-cell lymphoma 2, with a unique targeted mechanism of action that distinguishes it from other therapies. VenG increases the range of treatment options for patients unsuitable for FCR or BR, avoids the need for chemo-immunotherapy, and because of its fixed treatment duration enables patients to experience time without therapy. The ERG's clinical expert agrees that VenG is innovative.

1.8 No equality issues were identified by the company or the ERG. Patient and professional submissions highlight that restricting VenG to patients unsuitable for FCR or BR would deny younger 'fitter' patients access to a superior treatment that is better tolerated than existing options. The original NICE scope covered the broader population of patients with

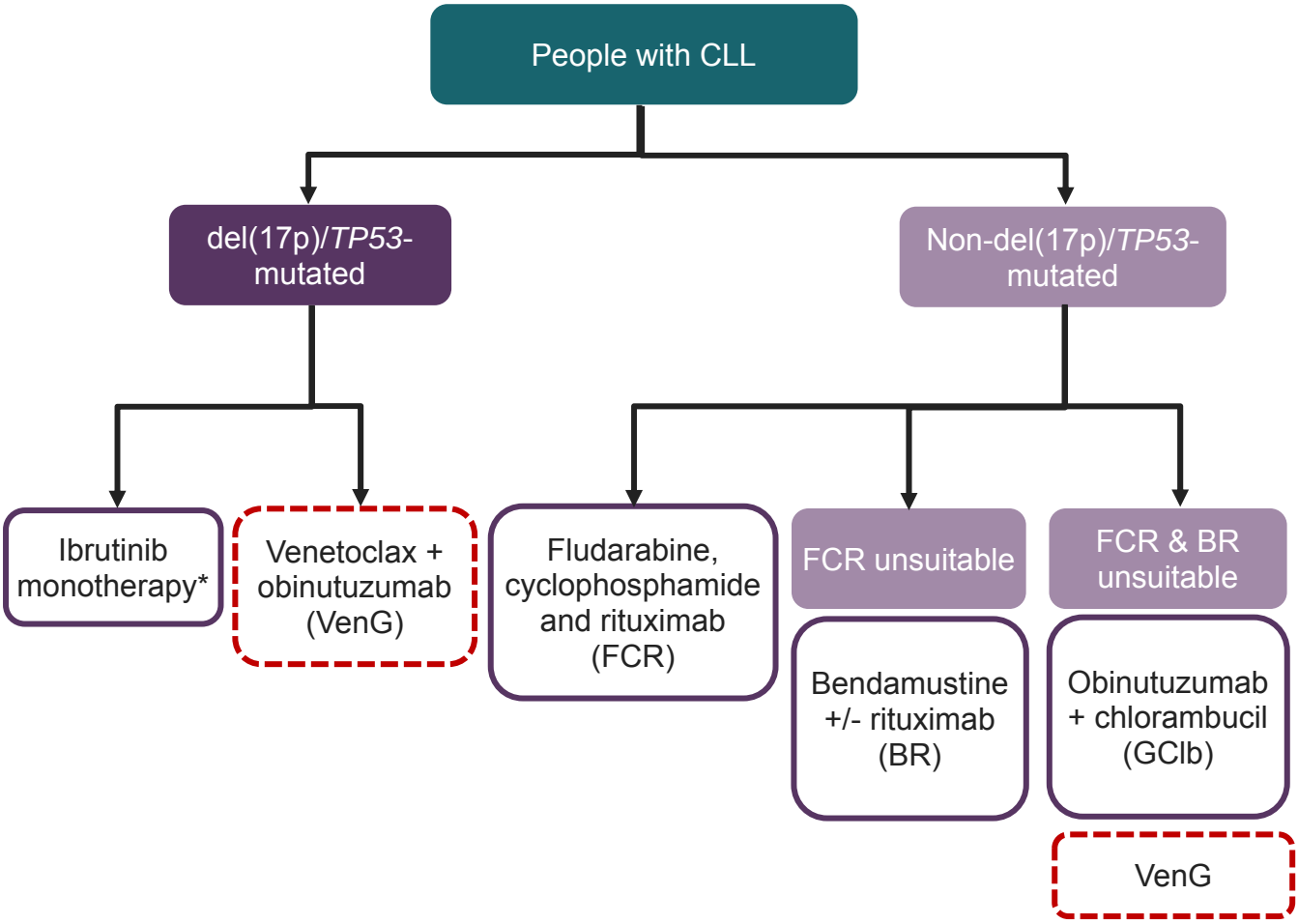
previously untreated CLL; however, the company did not submit evidence in patients suitable for FCR or BR.

2. Topic background

2.1 Disease background

- Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes).
- CLL is the most common of the chronic leukaemias, comprising 30% of all adult leukaemia. In England there were 3,157 new cases of CLL in 2017. The risk of developing CLL increases with age and is more common in men.
- CLL causes anaemia, swollen lymph nodes, spleen enlargement, weight loss and increased susceptibility to secondary cancers and infection. Fatigue is a common symptom, and the severity of fatigue is higher in CLL patients compared to published population norms and worsens as disease progresses.
- 5-year relative survival rates are around 70% and 75% for men and women, respectively.
- Treatment options for untreated CLL depend on factors such as stage of disease, performance status and co-morbidities. Most people will not have symptoms when they first receive a diagnosis, and in this case will not need any treatment.
- Approximately 5% to 10% of people diagnosed with CLL are considered to have 'high-risk' disease, characterised by the presence of cytogenetic mutations or abnormalities (that is, 17p deletion or *TP53* mutation). The presence of 17p deletion or *TP53* mutation can increase both the rate of cell growth and the resistance of the disease to chemoimmunotherapy, significantly reducing overall survival.
- Immunoglobulin heavy chain variable region (IGHV) mutations are found in around 60% of newly diagnosed and asymptomatic CLL patients. IGHV-mutated CLL is associated with a better prognosis, and is a powerful predictor of duration of response and overall survival with chemoimmunotherapy.

2.2 Proposed treatment pathway



* While NICE recommends idelalisib with rituximab for del(17p)/*TP53*-mutated patients, clinical experts consulted by both the company and the ERG agree that it has now been superseded by ibrutinib due to the higher risk of infection and death associated with idelalisib plus rituximab.

2.3 The technology

Marketing authorisation	Venetoclax (Venclyxto) received a positive CHMP opinion for the indication in this submission on 30 January 2020. Marketing authorisation was granted in March 2020.
Mechanism of action	Venetoclax is a first-in-class selective inhibitor of B-cell lymphoma 2 (Bcl2).
Indications	Venetoclax has a marketing authorisation for: • in combination with rituximab for treating adults with CLL who have received ≥1 prior therapy • as a monotherapy for treating adults with CLL who are unsuitable for or have failed on a B-cell pathway inhibitor, in the presence of a del(17p) or *TP53* mutation • as a monotherapy for treating adults with CLL who have failed on both chemoimmunotherapy and a B-cell pathway inhibitor, in the absence of a del(17p) or *TP53* mutation • in combination with obinutuzumab for treating adults with previously untreated CLL. **This marketing authorisation extension was granted in March 2020, and is the indication of interest in this submission.**
Administration	Venetoclax is administered orally as a film-coated tablet. The daily regimen is initiated on day 22 of Cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of Cycle 12. Obinutuzumab is administered intravenously for 6 cycles: • 1,000mg on Days 1, 8 and 15 of Cycle 1 (the first 1,000mg dose may be split over Days 1 and 2) • 1,000mg on Day 1 of Cycles 2–6.

2.4 Clinical evidence: key trials

Study	CLL-14
Design	Open-label, parallel, multicentre, Phase 3 study
Population	Patients with previously untreated CLL and coexisting medical conditions [redacted]
Location	Argentina (1), Australia (46), Austria (6), Brazil (22), Bulgaria (33), Canada (13), Croatia (12), Denmark (21), Estonia (5), France (39), Germany (54), Italy (26), Mexico (3), New Zealand (18), Poland (16), Romania (7), Russian Federation (41), Spain (30), Switzerland (3), **United Kingdom (8 across 6 sites)**, United States (28)
Intervention(s)	Venetoclax in combination with obinutuzumab
Comparator(s)	Chlorambucil in combination with obinutuzumab
Stratification factors	• Binet stage: A, B or C • Geographic region: US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; Latin America
Pre-planned exploratory subgroups	• Binet stage at screening (A, B, C) • Geographic region • Age (less than 75 years, greater than or equal to 75 years) • Gender (male, female) • Cytogenetic factors (deletion 17p, 11q and 13q, trisomy 12) • *TP53* status (deletion and/or mutation, none) • *IGHV* mutational status (unmutated, mutated)
Supports MA	Yes
Used in the model	Yes
Rationale for use in the model	• CLL-14 is the only study assessing venetoclax in combination with obinutuzumab in the relevant indication • CLL-14 informed the marketing authorisation application and considers a population directly relevant to the decision problem

2.5 **Clinical evidence: trial baseline characteristics in CLL14**

Characteristic		Venetoclax with obinutuzumab (n=216)	Chlorambucil with obinutuzumab (n=216)
Age	Median (range)	[redacted]	[redacted]
	Equal to or greater than 65 years	[redacted]	[redacted]
	Equal to or greater than 75 years, n (%)	72 (33.3)	78 (36.1)
Sex, n (%)	Male	146 (67.6)	143 (66.2)
	Female	70 (32.4)	73 (33.8)
Median time from diagnosis, months (range)		31.2 (0.4–214.7)	29.2 (0.3–244.8)
Binet stage, n (%)	A	46 (21.3)	44 (20.4)
	B	77 (35.6)	80 (37.0)
	C	93 (43.1)	92 (42.6)
ECOG performance status (%)	0	41.2	47.9
	1	45.8	40.5
	2	12.5	11.6
	3	0.5	0
Tumour lysis syndrome risk category, n (%)	Low	29 (13.4)	26 (12.0)
	Intermediate	139 (64.4)	147 (68.1)
	High	48 (22.2)	43 (19.9)
Total CIRS score greater than 6, n (%)		186 (86.1)	177 (81.9)
Estimated creatinine clearance greater than 70 ml/min, n/N (%)		128/215 (59.5)	118/213 (55.4)

Cytogenetic subgroup, %	Deletion in 17p	7.9	6.5
	TP53-mutated	[redacted]	[redacted]
	Del(17p)/*TP53*-mutated	[redacted]	[redacted]
	Non-del(17p)/*TP53*-mutated	[redacted]	[redacted]
	Del(17p)/*TP53*-mutation status missing	[redacted]	[redacted]
	IGHV-mutated	35.2	38.4
Comorbidities either frequently reported (more than 30% of patients), or imbalanced between arms, %	Vascular disorders	[redacted]	[redacted]
	Hypertension	[redacted]	[redacted]
	Metabolism and nutrition disorders	[redacted]	[redacted]
	Hypercholesterolaemia	[redacted]	[redacted]
	Gastrointestinal disorders	[redacted]	[redacted]
	Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
	Cardiac disorders	[redacted]	[redacted]
	Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
	COPD	[redacted]	[redacted]
	Asthma	[redacted]	[redacted]
	Psychiatric disorders	[redacted]	[redacted]
	Insomnia	[redacted]	[redacted]

2.6 **Clinical evidence: key trial results from CLL14**

Endpoint	Venetoclax with obinutuzumab (n=216)	Chlorambucil with obinutuzumab (n=216)
PFS		
Investigator-assessed PFS events, n (%)	[redacted]	[redacted]
1-year PFS probability, % (95% CI)	[redacted]	[redacted]
2-year PFS probability, % (95% CI)	88.17 (83.72, 92.61)	64.58 (57.95, 71.20)
3-year PFS probability, % (95% CI)	81.88 (76.50, 87.23)	49.51 (42.41, 56.60)
Median PFS	Not reached	35.6 ([redacted])
PFS hazard ratio (95% CI)	HR 0.31 (0.22, 0.44), p<0.0001	
OS		
OS events, interim analysis, n (%)	[redacted]	[redacted]
1-year OS probability, interim analysis, %	[redacted]	[redacted]
2-year OS probability, interim analysis, %	91.8	93.3
3-year OS probability, interim analysis, %	88.9	88.0
OS hazard ratio (95% CI)	HR 1.03 (0.60, 1.75), p=0.921	
Response rates		
Overall response rate at end of treatment, % (95% CI)	84.7 (79.2, 89.2)	71.3 (64.8, 77.2)
Complete response, n (%)	[redacted]	[redacted]
Time to next treatment		
TTNT events, n (%)	[redacted]	[redacted]

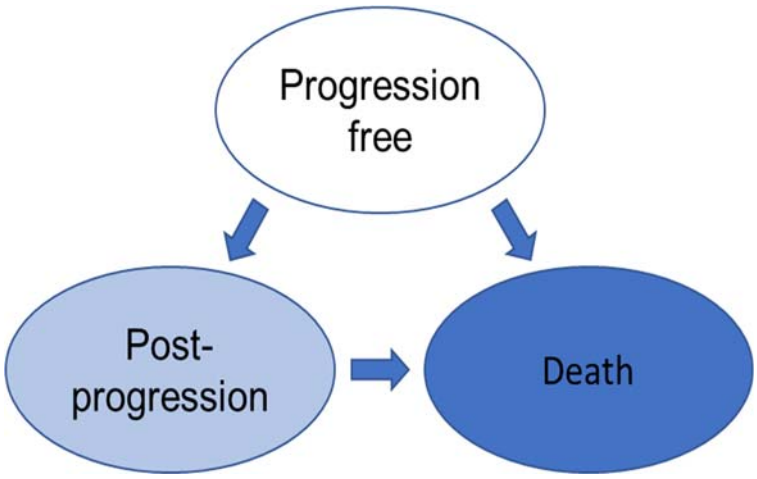
TTNT hazard ratio (95% CI)	HR 0.51 (0.34, 0.78), p=0.0012	
Undetectable minimal residual disease (uMRD) in peripheral blood		
uMRD at 18 months (%)	47.2	7.4
Difference in uMRD rates, % (95% CI)	[redacted]	

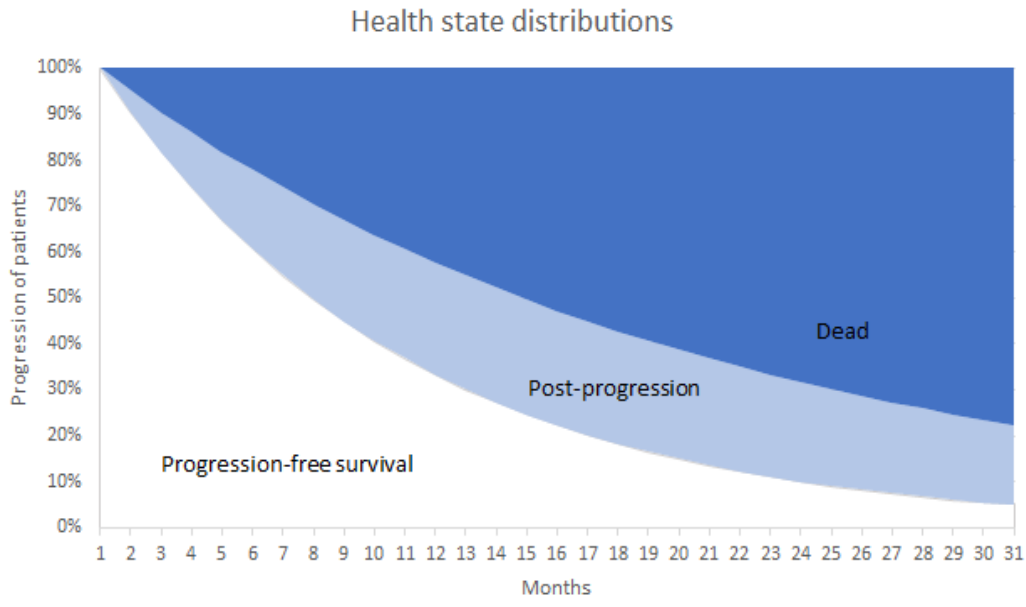
2.7 Indirect treatment comparison (compared with ibrutinib in previously untreated patients with a del(17p)/*TP53* mutation)

Endpoint	Unadjusted hazard ratio (ibrutinib compared with venetoclax with obinutuzumab)	95% confidence interval
PFS	0.660	0.270 – 1.615, p=0.363
OS	0.841	0.301 – 2.352, p=0.741

2.8 Model structure

- Partitioned survival model with 3 health states: progression-free, progressed disease, and death
- Time horizon of 30 years
- 28-day cycle length, with half-cycle correction
- NHS and Personal Social Services (PSS) perspective
- An annual discount rate of 3.5% for costs and benefits





2.9 Modelled survival (non-del(17p)/*TP53*-mutated population)

PFS modelling

Venetoclax with obinutuzumab				Chlorambucil with obinutuzumab			
3 year	5 year	10 year	20 year	3 year	5 year	10 year	20 year
Company: Independent log-logistic model							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG: Independent 2-knot hazard spline model							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS modelling

Venetoclax with obinutuzumab				Chlorambucil with obinutuzumab			
3 year	5 year	10 year	20 year	3 year	5 year	10 year	20 year
Company: Dependent exponential model							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG: Derived based on hazard rates from ERIC data from 3 years onwards*							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* See Issue 3 for further information.

2.10 Modelled time on treatment and time to next treatment (non-del(17p)/*TP53*-mutated population)

Time-to-next treatment modelling

Venetoclax with obinutuzumab			Chlorambucil with obinutuzumab		
5 year	10 year	20 year	5 year	10 year	20 year
Company: Independent log-logistic model					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG: Extrapolation derived based on a hazard ratio applied to the ERG's preferred PFS extrapolation					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.11 Modelled survival (del(17p)/*TP53*-mutated population)

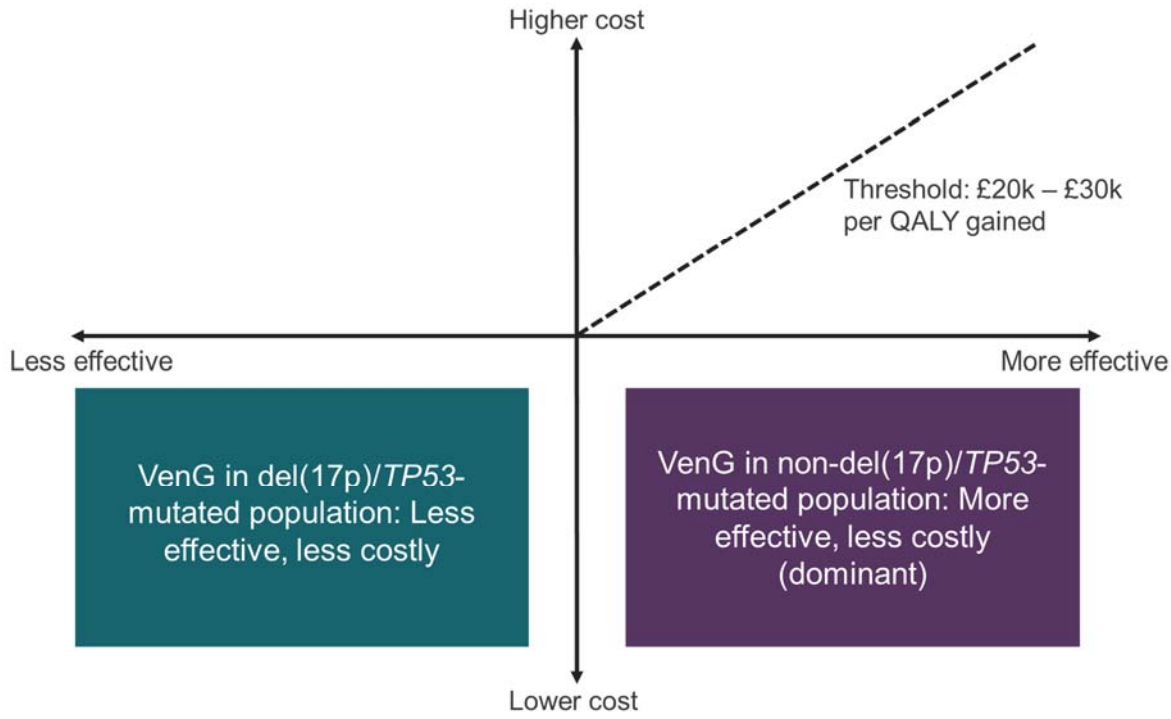
PFS modelling

Venetoclax with obinutuzumab				Ibrutinib			
3 year	**5 year**	**10 year**	**20 year**	**3 year**	**5 year**	**10 year**	**20 year**
Company: Independent log-logistic model, HR 0.66 in favour of ibrutinib							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG: Independent 1-knot hazard spline model, HR 0.66 in favour of ibrutinib							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS modelling

Venetoclax with obinutuzumab				Ibrutinib			
3 year	**5 year**	**10 year**	**20 year**	**3 year**	**5 year**	**10 year**	**20 year**
Company: Dependent exponential model, HR 0.84 in favour of ibrutinib							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG: Dependent 1-knot hazard spline model, HR 0.84 in favour of ibrutinib							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.12 Cost-effectiveness results (list prices)



VenG falls in the south east quadrant of the cost-effectiveness plane compared with GClb in the non-del(17p)/*TP53*-mutated population, and in the south west quadrant compared with ibrutinib in the del(17p)/*TP53*-mutated population. Technologies in the south east quadrant are dominant (more effective and less costly), and therefore cost effective.

For technologies in the south west quadrant, the ICER denotes cost savings per QALY foregone. For such technologies, the usual cost-effectiveness threshold applied by NICE of £20,000 to £30,000 per QALY gained is not meaningful.

An alternative approach for south west quadrant technologies is net monetary benefit (NMB), which represents the value of an intervention at a given cost-effectiveness threshold. NMB is calculated by multiplying the incremental effect by the cost-effectiveness threshold, and then subtracting the incremental costs. A NMB greater than zero indicates that the intervention is cost-effective at the cost-effectiveness threshold applied.

Cost-effectiveness results: Non-del(17p)/*TP53*-mutated population (list prices)

Treatment	Total		Incremental		ICER	NMB at threshold	
	Costs	QALYs	Costs	QALYs		£20k/QALY	£30k/QALY
Company base case							
GClb	[redacted]	6.742	N/A	N/A	Dominant	[redacted]	[redacted]
VenG	[redacted]	7.799	[redacted]	1.057			
ERG base case							
GClb	[redacted]	5.572	N/A	N/A	[redacted]	[redacted]	[redacted]
VenG	[redacted]	6.027	[redacted]	0.454			

Cost-effectiveness results: Del(17p)/*TP53*-mutated population (list prices)

Treatment	Total		Incremental		ICER	NMB at threshold	
	Costs	QALYs	Costs	QALYs		£20k/QALY	£30k/QALY
Company base case							
Ibrutinib	[redacted]	4.153	N/A	N/A	[redacted]	[redacted]	[redacted]
VenG	[redacted]	3.991	[redacted]	-0.163			
ERG base case							
Ibrutinib	[redacted]	3.690	N/A	N/A	[redacted]	[redacted]	[redacted]
VenG	[redacted]	3.326	[redacted]	-0.363			

* South west quadrant ICERs, which denote cost savings per QALY foregone, and should not be considered in the same manner as north east quadrant ICERs.

3. Key issues for consideration

Issue 1 – Patient population

Questions for engagement	a) Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal? b) Is the patient population in the CLL14 trial appropriate for decision-making given the small number of UK patients?
Background/description of issue	a) **The company** submission limits the positioning of VenG to the following 2 subpopulations: 1. previously untreated FCR or BR-unsuitable patients with CLL without del(17p)/*TP53* mutation, and 2. previously untreated patients with CLL with del(17p)/*TP53* mutation. Only patients with multiple co-existing medical conditions were recruited in CLL14, defined either by a cumulative illness rating scale (CIRS) greater than 6 or creatinine clearance (CrCl) less than 70 in patients not meeting the CIRS criterion. The company considers that in the UK NHS context such patients would typically be considered unsuitable for FCR or BR. The company's positioning is narrower than the EMA marketing authorisation indication and the final scope issued by NICE, both of which cover patients with previously untreated CLL. Due to the restricted patient population the company considers neither FCR nor BR to be a relevant comparator, despite them being included in the NICE scope. Although the EMA marketing authorisation is for the broad previously untreated patient population, the company considers it unlikely that in NHS clinical practice VenG will be used in patients suitable for FCR or BR. This assumption was agreed by consensus among five UK clinical experts consulted at a company-sponsored advisory board in April 2019. The subpopulation of FCR or BR-unsuitable patients with previously untreated CLL without del(17p)/*TP53* mutation also aligns with the patient population of the company's primary source of clinical effectiveness evidence, the CLL14 trial.

	The second subpopulation was selected by the company as it is reflective of CLL14, in which around 10% of patients had del(17p)/*TP53* mutation, and is also a patient population with a poor prognosis and a high unmet need. **The ERG's** clinical expert considers that in UK clinical practice clinicians are keen to use VenG as a treatment option for patients younger or fitter than those in CLL14. In addition, the inclusion criteria used to define coexisting medical conditions that would typically mean patients are unsuitable to receive FCR or BR (CIRS score greater than 6, CrCl less than 70mL/min) are not often used in UK clinical practice. The ERG's clinical expert stated that in the UK there is no standard assessment to determine suitability for FCR or BR, and patients with CLL are assessed individually. As such, it is likely that some of the patients included in CLL14 may in fact be eligible for FCR or BR treatment in the UK. b) **The ERG** notes that CLL14 was an international trial undertaken in 21 countries, of which there were 6 UK sites and only 8 UK participants. This may limit the generalisability of the data to the NHS population. The ERG also comments that in the company's submission, the entire CLL14 trial population (which included patients with and without del(17p)/*TP53* mutation) was used as evidence for the subpopulation without del(17p)/*TP53* mutation. Although the number of patients with del(17p)/*TP53* mutation in CLL14 was small (25 patients out of 216 in the VenG arm), the ERG is unable to comment on how the inclusion of these patients may bias the results.
Why this issue is important	The patient populations used in the analysis should reflect how the technology will be used in UK clinical practice, and be representative of the intended target subgroup(s). If patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation are considered a relevant population, FCR and BR would be considered relevant comparators for the appraisal. The company does not have clinical data in patients suitable for FCR or BR.
Technical team preliminary judgement and rationale	Given that: • the EMA marketing authorisation indication for VenG is for previously untreated patients with CLL

	• in UK clinical practice physicians are likely to want to use VenG in patients other than those included in CLL14, and • there is some variation across the UK in how patients are assessed to be suitable for FCR or BR, the technical team is concerned that VenG would be used in a broader patient population than that recruited in CLL14 if it is shown to be cost-effective in the subgroup of previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation, and recommended by NICE on this basis. This concern is supported by comments from professional organisations, which recommend that 'fit' patients suitable for FCR or BR should be given the option to use VenG due to its superior tolerability profile. The committee requests that the company provide a comparison of VenG with FCR and BR in the non-del(17p)/*TP53*-mutated patient population suitable for FCR or BR. The technical team would also prefer the analysis for the population without del(17p)/*TP53* mutation to be conducted using the CLL14 data from this subgroup alone, rather than the mutated and non-mutated populations combined. However, the number of mutated patients in each treatment arm is balanced: n=25 in the VenG arm and n=24 in the GClb arm. The technical team is also concerned by the small number of UK patients recruited for CLL14. This may impact the OS results in particular, given that a large proportion of the sample was comprised of patients from developing countries where access to more expensive later-line therapies (e.g. venetoclax plus rituximab, ibrutinib) may be more limited and background mortality rates are different.

Issue 2 – The most plausible PFS extrapolation: Non-del(17p)/TP53-mutated population

Questions for engagement	Which PFS extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?
Background/description of issue	**The company** submission presents the CLL14 PFS results from the most recent data cut (August 2019) after a median follow up of 39.6 months. At this point, the median PFS had not been reached in the VenG arm. In the GClb arm, the median PFS was 35.6 months (95% CI [redacted] to [redacted]). To generate the 30-year PFS data required for the cost-effectiveness model, the company tested several parametric PFS extrapolations fitted independently to each arm of the observed CLL14 PFS data: exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz curves. In the company's cost-effectiveness model, these extrapolations were subjected to 2 constraints: 1. there could not be more patients in the PFS health state than there were alive, and 2. the hazard rate of disease progression could not fall below the hazard rate of background mortality. Clear differences are evident for the PFS extrapolations depending on the curve that is used, particularly for the VenG extrapolations (see Figure 1, in which the constraints detailed above have not been applied).

Figure 1. Parametric extrapolations for PFS for VenG and GClb (independent model)

Source: Figure 20, Addendum to company submission

The company determined that the Gompertz model provided the best statistical fit for the VenG extrapolations, and a log-logistic model provided the best statistical fit for the GClb extrapolations. However, the company placed limited weight on statistical fit due to the immaturity of the data, and primarily used external data and clinical input to select the most appropriate survival curves. On this basis, the Gompertz model was rejected by the company as it produced unrealistic projections that underestimate PFS in both arms (see Table 1).

CLL11 (the pivotal trial used in NICE TA343) provides 5-year PFS data for GClb in a similar patient population to that of CLL14. For the GClb arm of CLL14, the log-logistic and Weibull curves most closely align with the long-term follow-up data from CLL11 (where 23% of patients treated with GClb were in PFS after 5 years). Of the two models, the log-logistic model was selected by the company as it: 1) provides a good fit to the 5-year PFS data for GClb from CLL11; 2) is supported by an assessment of hazard rates over time (although limited detail is provided by the company as to how

this assessment was made); and 3) was validated by clinical experts that it most closely resembles what is seen in clinical practice for GClb.

Table 1. PFS predictions from parametric models fitted to CLL14 trial data and benchmarks

Distribution	VenG				GClb			
	3 year	5 year	10 year	20 year	3 year	5 year	10 year	20 year
Company-tested extrapolation models (preferred highlighted in bold)								
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
External references								
CLL11 (95% CI)					42%	25% (19-31)		
ERIC study					42%			
CLL14	81.9%				49.5%			
ERG clinical expert	75%	50%	20%	5%	40%	25%	0%	0%
ERG-preferred model								
2-knot hazard spline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 25, Final ERG report

	Citing advice from the NICE DSU technical support document to use the same curve between treatment arms, the company opted to fit a log-logistic model to both the VenG and GClb data. The company rejected the exponential curve, as selecting it for both treatment arms would mean assuming proportional hazard rates which the company had concluded to be false. **The ERG** agrees with the company that the hazard rates are not proportional between treatment arms, and thus that an independent model should be used and an exponential model can be rejected. The ERG also agrees that statistical fit cannot be relied on when the data are so immature. However, the ERG notes that the company's independent models all overestimate the 3-year PFS rate predictions in the GClb arm in particular compared to the available 3-year PFS data from CLL11, CLL14 and the ERIC study, as well as the opinion of the ERG's clinical expert (see Table 1). The ERIC study was a retrospective multi-centre study assessing obinutuzumab with or without chlorambucil in a similar 'unfit' untreated patient population to CLL14. ERIC included 437 patients recruited from Europe, Israel, Canada and Argentina. The ERG also considers that the company failed to provide sufficient justification for selecting the log-logistic curve, noting that with the above constraints removed, the hazard rates for PFS decrease over time when a log-logistic curve is applied, falling below background mortality. The ERG considers this clinically implausible, as OS events are included in this measure. In addition, the ERG compared the mean PFS duration from the company's log-logistic extrapolation for GClb from CLL14 to the mean PFS duration from the appraisal of GClb based on the longer-term CL11 data. The mean PFS duration of [redacted] years based on the CLL14 data compared to 2.83 years based on CLL11 shows the log-logistic extrapolation appear to be a substantial overestimate. The ERG is reluctant to recommend any of the company's independent PFS extrapolations due to their implausibility, and the immaturity of the data. After investigating 60 other different PFS models,

	the ERG considers an independent 2-knot hazard spline model to be most plausible from the current data, for the following reasons (see Table 1): 1. it predicts a 5-year PFS rate of [redacted] for GClb, the closest of all the models to the observed data from CLL11 2. it estimates a mean PFS duration of [redacted] years, closer than the company's base-case to the 2.83 years observed in CLL11 3. it produces a 10-year estimate for VenG close to that of the ERG's clinical expert.
Why this issue is important	There are clear differences between the PFS extrapolations depending on the selected model, with these differences particularly notable for the VenG arm. To be able to assess the clinical- and cost-effectiveness of VenG, it is important to identify the most appropriate way of estimating the PFS of both VenG and GClb. The choice of extrapolation is likely to drive costs and QALYs in the model.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG that the company's extrapolations all overestimate the 3-year PFS for GClb based on available reference data sources, and the 3-year PFS for VenG based on the observed data from CLL14. On balance, the technical team considers the ERG's 2-knot hazard spline model preferable to the company's base-case log-logistic model as it: 1. provides GClb extrapolation estimates marginally closer to the observed data from CLL11, and closer to the estimations of the ERG's clinical expert 2. provides VenG extrapolation estimates closer to that of the ERG's clinical expert at the 5-, 10- and 20-year timepoints, with a noticeably more conservative and clinically plausible figure of [redacted] at 10 years compared to the [redacted] estimated from the company's log-logistic model 3. estimates a mean PFS duration closer to the observed CLL11 data than the company's base-case. The technical team notes, however, that the ERG's model gives the highest 3-year VenG estimate of all the models tested by either the ERG or the company.

Issue 3 – The most plausible OS extrapolation: Non-del(17p)/TP53-mutated population

Questions for engagement	Which overall survival (OS) extrapolation model is most plausible for GClb in the patient population without del(17p)/*TP53* mutation?
Background/description of issue	OS was assessed as a secondary endpoint in CLL14. At the most recent data cut (August 2019) the median OS had not been reached in either treatment arm, and there was no evidence of a difference between treatment arms. The positioning of VenG in patients with previously untreated CLL means that OS is likely to be confounded by treatments for relapsed or refractory CLL. **The company** considers the OS data from CLL14 too immature to be meaningful. However, after exploring several approaches, including using the longer term CLL11 trial data to model OS, the company considers the best source of evidence for the OS estimates to be the CLL14 trial. There was little evidence to support a treatment effect on OS, and the assumption of proportional hazards between treatments was accepted by the company based on testing and a visual inspection of the logarithm of the cumulative hazard function. A dependent model was therefore preferred by the company as its base case. The company's tested OS extrapolations are shown in Figure 2 below, prior to the application of the background mortality constraint.

Figure 2. Parametric extrapolations for OS for VenG and GClb (dependent model)

Source: Figure 21, Addendum to company submission

Both the log-normal model and exponential model were found to provide a good statistical fit to the observed data. The exponential model was selected by the company as the hazard function decreased over time for the log-normal model, which was considered unrealistic. The company used the same GClb OS curve for both treatment arms, on the basis that post-progression survival following initial treatment is likely to be similar given the availability of innovative treatments in later lines which have a greater impact on OS than first-line treatments. Clinical experts consulted by the company considered this a conservative approach, as undetectable MRD levels were significantly higher in the VenG arm than the GClb arm, which would normally translate to a better long-term OS.

Similar to the PFS and TTNT extrapolations, the OS estimates were restricted by background mortality. The company's modelling approach was validated by clinical and health economic experts, and by comparison with the following post-progression survival (PPS) estimates:

1) **5-year follow-up data from CLL11.** The OS curves generated from CLL11 were found to lie well below the observed and extrapolated curves from CLL14. The company reasoned that this

discrepancy was due to the lack of effective subsequent therapies during CLL11, and the fact that Clb was given for 6 more cycles in CLL14 compared with CLL11.

2) **The ibrutinib arm from the RESONATE trial.** Again, the OS curve from this data lies below the observed and extrapolated curves from CLL14, though above those from CLL11. The high proportion of patients with del(17p) mutation (30%) was considered by the company to explain this difference, as this patient subgroup has poorer outcomes than the non-mutated population.
3) **The ibrutinib arm generated using the Warwick ERG's NMA from TA561.** This OS curve lies above that from CLL14 but is relatively close to the CLL14 PPS data.

The company observed that the extrapolated OS curves based on the CLL14 data are close to those of the general population generated from UK life tables. Clinical experts consulted by the company considered this reasonable given the age and comorbid nature of the CLL14 trial population, as patients would be increasingly likely to die from causes unrelated to CLL.

The ERG notes that all the extrapolation models tested by the company produced very similar extrapolations (see Table 2), despite the considerable uncertainty associated with the immature OS data. This similarity is due to the constraint that the hazard rate cannot fall below background mortality, which comes into effect from around 4.87 years in all the company's models. As such, the ERG considers that none of the company's models would be plausible without this constraint. The company's modelling of OS implies that there is no additional risk of death from CLL compared to the general population, which the ERG's clinical expert states to be untrue. The ERG also comments on the considerable difference between the company's predicted OS curves and the 5-year follow-up data from CLL11 despite the subsequent availability of newer therapies, and is reluctant to select any of the extrapolation curves proposed due to their implausibility and reliance on the background mortality constraint.

Table 2. OS predictions from dependent parametric models for the non-del(17p)/*TP53*-mutated population

Distribution	GClb (also used for VenG)			
	3 year	5 year	10 year	20 year

Company-tested extrapolation models				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
External references				
Background mortality	[redacted]	[redacted]	[redacted]	[redacted]
CLL11 GClb	[redacted]	[redacted]	[redacted]	[redacted]
ERIC Study GClb	[redacted]	[redacted]	[redacted]	[redacted]
ERG Clinical Expert	[redacted]	[redacted]	[redacted]	[redacted]
ERG-preferred model				
OS using ERIC hazard rate from 3 years	[redacted]	[redacted]	[redacted]	[redacted]

Source: Adapted from ERG Final report, Table 27

The ERG explored 60 alternative models, but none predicted a 5-year survival of below 80% (in comparison to a 5-year survival of [redacted] in CLL11). As such, the ERG did not consider any of them to be consistent with the CLL11 data.

	The ERG then obtained patient-level OS data from the ERIC study previously described, and recreated the patient-level OS data from CLL11, before exploring fitting exponential models to the data from each study to investigate the hazard rates. To obtain an extrapolation model consistent with both CLL14 and the external study data, the ERG modelled the hazard rate from CLL14 for the first 3 years, followed by an exponential model fitted to the hazard rate from ERIC after this point. The ERG favoured ERIC over CLL11 as ERIC is more recent and likely to better represent the OS impact of later lines of therapy. Using the ERG's preferred OS extrapolation, the background mortality constraint comes into effect after 14 years, substantially later than the 4.87 years in the company's models. The ERG agrees with the company's assumption of equal OS between the VenG and GClb treatment arms. Despite VenG's PFS benefit there is no clinical evidence to support an OS difference, and the ERG's clinical expert commented that no evidence is available on the efficacy of subsequent treatments following first-line VenG, while ibrutinib has been demonstrated to be effective after GClb. As such, there is a possibility that the assumption of equal OS may be negatively biased against GClb.
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of VenG, it is important to identify the most appropriate way of estimating the OS of both VenG and GClb. The choice of extrapolation is likely to drive costs and QALYs in the model.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG and the company that the data suggest there is no OS difference between treatment arms based on the current data cut, and that the same curve should be applied to both treatments. The technical team considers that on balance this is likely to be a conservative approach given VenG's benefit in terms of PFS and MRD negativity, despite the ERG's concern that it may be negatively biased against GClb. The technical team also agrees that the company's OS extrapolation models align very closely with background mortality and appear strongly dependent on this constraint, as greater separation between the curves would be expected otherwise given the immaturity of the OS data. As such, the company's curves effectively assume that the OS of patients with CLL is the same as that of the general population, which does not appear clinically plausible.

	The technical team notes that the ERG's OS extrapolation model aligns better with the CLL11 data at 5 years than any of the company's models, and is also more in line with the estimates of the ERG's clinical expert at each timepoint (with the exception of the company's Gompertz model at 20 years). As such, the technical team considers the ERG's model to be the most clinically plausible.

Issue 4 – Subsequent treatment costs

<table>
<tr><td>Questions for engagement</td><td>a) Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?
b) Which TTNT extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/TP53 mutation?</td></tr>
<tr><td>Background/description of issue</td><td>a) In the company's economic model, the proportion of patients receiving subsequent second-line treatment (and accruing the associated costs) is calculated by subtracting the TTNT curve from the OS curve for the non-del(17p)/TP53-mutated subgroup, and the PFS curve from the OS curve for the del(17p)/TP53-mutated subgroup. The company applied the following base case subsequent treatment mix in its model, informed by the literature and clinical input:

<u>Table 3. Subsequent treatment mix and durations used in the model</u>
<table>
<tr><th rowspan="2">Initial treatment</th><th colspan="2">Subsequent treatment (mean duration shown in brackets, months)</th></tr>
<tr><th>Non-del(17p)/TP53 mutation</th><th>Del(17p)/TP53 mutation</th></tr>
<tr><td>VenG</td><td>50% ibrutinib (30); 50% VenR (24.4)</td><td>100% ibrutinib (39)</td></tr>
<tr><td>GClb</td><td>50% ibrutinib (30); 50% VenR (24.4)</td><td>N/A</td></tr>
<tr><td>Ibrutinib</td><td>N/A</td><td>100% venetoclax monotherapy (16)</td></tr>
</table>
Source. Adapted from Tables 56 and 57, company submission. VenR = venetoclax with rituximab

As described in Table 3, subsequent treatment durations are 24.4 months for VenR, 39 months for ibrutinib and 16 months for venetoclax monotherapy based on the literature.

These mean treatment durations are used to calculate an average cost per cycle for regimens where dosing varies between cycles (e.g. VenR). For regimens with a fixed per-cycle cost (e.g. ibrutinib), varying the mean treatment duration has no impact on the average cost per cycle. In the model, patients progressing onto second-line treatment are not constrained to receive it for the treatment durations specified in Table 3. Instead, second-line treatment costs are modelled continuously until death, regardless of the treatment durations inputted.</td></tr>
</table>

	The company argues that it would not be feasible to calculate a treatment sequencing model to best reflect duration and lines of therapy in the relapsed / refractory (R/R) CLL setting. Given the lack of published evidence on the use of R/R treatments on CLL patients with comorbidities, the company decided that the fairest approach would be to calculate the costs for both arms continuously using a basket of costs until end-of-life care costs apply. The company argues that this approach does not favour either treatment arm. **The ERG**'s clinical expert confirmed that the treatments in Table 3 are consistent with what is offered in UK clinical practice, though highlighted that VenR is becoming more popular and is likely to be offered to around 80% of patients after first-line treatment in future. Changing these proportions has minimal impact on the overall incremental results. While acknowledging the lack of data on treatment sequencing in R/R CLL, the ERG queried the company's approach to modelling the second-line treatment costs, considering it unconventional and not ideal. The ERG noted that the average time on treatment for second-line treatments in the GClb arm was 5.3 years in the company's model, compared to 3.25 years and 2.03 years for ibrutinib and VenR, respectively, based on the literature provided by the company. The ERG also highlighted that the company's approach does not account for gaps between different treatment lines. The ERG considers that the way the subsequent treatment costs have been modelled by the company is likely to be somewhat biased against GClb, although the extent to which this is the case is unclear. In response to a query from the ERG, the company provided information on the interventions received as later lines of therapy by patients in CLL14. The most common second-line treatment was [redacted], with a median treatment duration of [redacted] in patients receiving GClb as a first-line treatment, and [redacted] in patients receiving VenG as a first-line treatment. **The company** tested several independent extrapolation models to the observed TTNT data from CLL14. In the same manner as the PFS extrapolations, the TTNT extrapolations were subject to constraints:

1. the number of patients who had not begun their next treatment could not exceed the number of patients alive, and
2. the hazard rate of beginning next treatment could not fall below the hazard rate of background mortality.

The company determined the exponential model to be the best statistical fit for the VenG arm and the log-logistic model the best statistical fit for the GClb arm. However, given the substantial variation evident between the TTNT model estimates for 10 years and beyond in the GClb arm in particular (see Table 4), the company again used the CLL11 trial as an external validation source. CLL11 reports that after 5 years, [redacted] (95% CI [redacted] to [redacted]) of patients treated with GClb had not experienced a TTNT event. Based on this, the company selected the log-logistic curve as it is relatively close to the observed CLL11 data, and it also agrees with the company's choice of curve for PFS, an outcome closely correlated with TTNT. Furthermore, the company noted that the log-logistic distribution is associated with decreasing hazards over time, which aligns with the clinical expectation that the longer a patient remains in remission, the less likely they are to require a subsequent line of therapy. However, there is some discrepancy in the company's submission on this point. Notably, in the company's original submission (versus an updated addendum provided in August 2019) the log-logistic curve was rejected as the assumption of decreasing hazard rates over time was deemed clinically implausible.

Table 4. TTNT predictions for non-del(17p)/*TP53*-mutated patients

Distribution	VenG			GClb		
	5 year	10 year	20 year	5 year	10 year	20 year
Company-tested extrapolation models						
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
External references						
CLL11 Data	-	-	-	[redacted]	-	-
ERG-preferred model						
ERG hazard ratio on PFS extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 26, ERG Final report

The ERG does not support the use of a log-logistic curve to model TTNT, or any of the other independent extrapolations tested by the company, as none of them produce a 5-year TTNT estimate for GClb in line with that observed in CLL11 (see Table 4). The ERG also considers the data too immature to fit the extrapolation models with any degree of certainty, and notes that the models are reliant on the background mortality constraint, casting doubt on their reliability.

The ERG investigated 60 alternative dependent and independent models to try to find more plausible estimates. While 2 independent 2-knot spline models produced 5-year GClb TTNT estimates close to that observed from CLL11, when applied to the VenG arm they remained dependent on the background mortality constraint and were thus rejected by the ERG.

Searching for an alternative approach, the ERG explored whether an assumption of proportionality held between TTNT and PFS, given the similarity between the two outcomes. The cumulative hazard plots suggest this to be the case (see Figure 3), and so the ERG applied the resulting hazard ratio between TTNT and PFS to the ERG-preferred PFS curve in the economic model. The resulting TTNT extrapolation was closer to the observed 5-year CLL11 GClb data than any other model and within its 95% confidence interval (see Table 4 above). It was also far less dependent on the background mortality constraint. As such, the hazard ratio approach is the ERG's preferred choice for the TTNT extrapolation.

	Figure 3. Cumulative hazard plots, PFS and TTNT  Source: ERG Final report, Figure 3
Why this issue is important	The difference in the acquisition cost of subsequent treatments between arms is a key driver in the economic model. As such, it is important that the length of time that subsequent treatment is received for accurately reflects UK clinical practice. The TTNT curves determine the timepoint at which patients begin to receive subsequent treatment in the economic model, and are subject to a large degree of uncertainty.
Technical team preliminary judgement and rationale	a) The technical team is concerned that the company's model currently overestimates the costs of subsequent treatments, as the modelled treatment durations are much longer than is reported in the literature and may not reflect clinical practice. The company's approach may unfairly bias GClb, where the risk of patients experiencing a TTNT event is increased compared to GClb, but the same OS curve is applied to both arms. The technical team requests that the company provide a revised version of the economic model in which the duration of subsequent treatments is constrained by the figures reported in the literature. b) The technical team notes that while there is substantial variation between the company's tested 20-year PFS extrapolations for VenG, the company's TTNT extrapolations do not appear to be subject to the same degree of variation, with an absolute difference of just [redacted] between the highest and lowest estimates. This suggests, as the ERG also states, that the company's

models are likely to be heavily reliant on the background mortality constraint. Given that TTNT and PFS can be expected to be similar, the company's estimations of [redacted] for VenG at 20 years appear implausibly high given the estimation of the ERG's clinical expert of a PFS of 5% at the same timepoint. The technical team also disagrees with the company's assertion that the decreasing hazard rate over time associated with their log-logistic distribution is clinically plausible.

The technical team agrees with the ERG's revised modelling approach. The assumption of proportional hazard rates between the TTNT and PFS outcomes appears to hold based on Figure 3, and the ERG's model is closer to the 5-year GClb data from CLL11 than any of the company's models. In general, it produces lower TTNT estimates than the company's models in both treatment arms, which appear more clinically plausible when compared to the technical team's preferred PFS extrapolation (see Table 5).

Table 5. Comparison of PFS and TTNT extrapolations

Distribution	VenG			GClb		
	5 year	10 year	20 year	5 year	10 year	20 year
Technical team-preferred PFS model						
ERG's 2-knot hazard spline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG-preferred TTNT model						
ERG hazard ratio on PFS extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company-tested TTNT extrapolation models						
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Source. Adapted from ERG final report, Tables 25 and 26						

Issue 5 – Indirect comparison hazard ratios: Del(17p)/TP53-mutated population

Questions for engagement	Which PFS and OS hazard ratios are most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation?
Background/description of issue	In the CLL14 trial, 25 patients of a total of 216 in the VenG arm were del(17p)/*TP53*-mutated. At the data cut-off (August 2019), [redacted] PFS events had taken place in these patients. Less than 10% of patients with previously untreated CLL have del(17p)/*TP53* mutation, presenting trial recruitment challenges and resulting in a general lack of data for this population. CLL14 provided head-to-head comparative data for VenG versus GClb only. No comparative data was generated against ibrutinib, the relevant comparator, in patients with del(17p)/*TP53* mutation. As such, an indirect comparison is required. **The company** conducted an SLR to support an indirect comparison against ibrutinib in patients with previously untreated del(17p)/*TP53*-mutated CLL. 3 studies were identified: 1. A phase 2 single-arm study (Farooqui, 2015) with a 5-year follow-up (Ahn, 2018) 2. A real-world evidence study (Mato, 2018) that assessed efficacy in patients excluded from RESONATE 2 (a trial of ibrutinib versus Clb in previously untreated CLL) because they had del(17p)/*TP53* mutation 3. A phase 3 randomised trial (ALLIANCE) The company excluded the ALLIANCE data as it included only 9 patients with del(17p) mutation. A feasibility assessment was then conducted to determine the potential to conduct a MAIC of VenG versus ibrutinib using the remaining identified trial data. As there was no common comparator between VenG and ibrutinib in the trials identified by the SLR, any indirect comparison would need to be unanchored. The company concluded that an unanchored MAIC would not be feasible for the following reasons: • None of the studies identified in the SLR reported sufficient prognostic characteristics for the del(17p)/*TP53*-mutated population to allow a meaningful MAIC to be conducted: - Ahn (2018) and Farooqui (2015) do not report on variables including age, gender and *IGHV* mutation status for the del(17p)-mutated group

	- Mato (2018) does not provide any information on baseline prognostic factors - CIRS score, used in CLL14 to determine unsuitability for FCR or BR treatment, is not reported in any of the studies - The company unsuccessfully attempted to contact the authors of the publications above to obtain further information on baseline characteristics. • Matching and weighting patients in the MAIC reduces the effective sample size. The findings from the MAIC are likely to suffer from a lack of statistical power due to the small sample size. Rather than a MAIC, the company instead opted for an unadjusted naive indirect comparison. The company considered Mato (2018) to be the preferred study for the base-case comparison as it has the largest sample size: 110 patients with del(17p)/*TP53* mutation, compared with 51 in Farooqui (2015) and 86 in Ahn (2018). Farooqui (2015) was excluded as Ahn (2018) provides more recent evidence from the same trial. The company also provides an alternative unadjusted naive indirect comparison against Ahn (2018). Since individual patient data (IPD) and hazard ratios (HRs) were not available from Mato (2018), the company simulated these by digitising the available KM curves and applying the methodology developed by Guyot et al[1]. Other than excluding non-del(17p)/*TP53*-mutated patients, no other adjustments were made to the data to account for differences between the study populations. The company noted that compared with CLL14, Mato (2018) included younger patients which could favour ibrutinib in the comparison with VenG. The results of the base-case indirect comparison show a PFS HR of 0.660 in favour of ibrutinib. This is not statistically significant and has wide confidence intervals (95% CI 0.270 – 1.615; p=0.363). Similarly, the OS HR of 0.841 favours ibrutinib, but again this is not statistically significant and has wide confidence intervals (0.301 – 2.352; p=0.741). The company stated that the HRs cannot be considered reliable or robust, and noted that the assumption of proportional hazards between treatment arms does not hold.

[1] Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9

	The results of the alternative indirect comparison using the Ahn (2018) data show a PFS HR of [redacted] (95% CI [redacted] to [redacted]; p=[redacted]) [redacted], which is not statistically significant. The OS HR of [redacted] (95% CI [redacted] to [redacted]; p=[redacted]) [redacted], but not at a statistically significant level. In response to a request from the ERG, the company performed an additional analysis indirectly comparing VenG to ibrutinib using the ibrutinib PFS data pooled across Mato (2018), Ahn (2018) and ALLIANCE, and the ibrutinib OS data pooled across Mato (2018) and Ahn (2018). The results were similar to the comparisons using the individual study data, with a PFS hazard ratio of [redacted] (95% CI [redacted] to [redacted]; p=[redacted]) [redacted], and an OS hazard ratio of [redacted] (95% CI [redacted] to [redacted]; p=[redacted]) [redacted]. **The ERG** notes considerable heterogeneity between the populations of the studies identified by the SLR and that of CLL14 in terms of study design, eligibility criteria and outcomes, with the heterogeneity of patient baseline characteristics unknown. The ERG considers that the comparability of the del(17p) subgroup of Mato (2018) and the del(17p)/*TP53*-mutated subgroup from CLL14 cannot be ascertained, and notes several inaccuracies in the description of Mato (2018) by the company. Overall, the ERG agrees with the company that the patients in the Mato (2018) subgroup are likely to be younger and fitter than those of CLL14. Similarly, the comparability of the del(17p)/*TP53*-mutated subgroup of Ahn (2018) with the del(17p)/*TP53*-mutated subgroup from CLL14 cannot be ascertained by the ERG. Again, the ERG notes several inaccuracies in the description of Ahn (2018) by the company, most notably the sample sizes included in the analysis. The ERG concludes that the subgroup from Ahn (2018) are likely to be younger, have fewer comorbidities and fewer men. Overall, given the considerable heterogeneity between studies and the wide confidence intervals associated with the results, the ERG considers the indirect comparison presented by the company to be inadequate for providing any meaningful information to compare VenG with ibrutinib in terms

	of their impact on PFS or OS in patients with del(17p)/*TP53* mutation. The ERG is unable to conclude whether the additional analysis based on the pooled ibrutinib data can be considered any more reliable than the comparisons based on the individual ibrutinib study data. Ultimately, the ERG applied the PFS and OS hazard ratios from the company's base-case comparison with Mato (2018) when deriving the VenG extrapolations (see Issue 6), in the absence of a better alternative.
Why this issue is important	It is important to establish the clinical effectiveness of VenG compared with ibrutinib in patients with previously untreated del(17p)/*TP53*-mutated CLL to be able to estimate its cost-effectiveness.
Technical team preliminary judgement and rationale	The technical team notes the ERG's concerns regarding the likely high (and unknown) degree of heterogeneity between the patient populations of the trials included in the company's indirect comparison. While all the indirect comparisons conducted by the company and requested by the ERG appear to [redacted], the technical team notes that the ERG considers the populations from Mato (2018) and Ahn (2018) to be fitter than that of CLL14. This would bias the comparisons against VenG, although the degree to which this is the case is unknown. The PFS and OS hazard ratios derived from the comparison with Mato (2018) [redacted]. Given the bias previously mentioned, the technical team considers that on balance these figures are most appropriate to include in the cost-effectiveness model, but considers them to be associated with a substantial degree of uncertainty.

Issue 6 – OS and PFS extrapolations: Del(17p)/TP53-mutated population

Questions for engagement	Do you agree with the company's approach to modelling the OS and PFS curves for VenG and ibrutinib in patients with del(17p)/*TP53* mutation?
Background/description of issue	**The company** applied a covariate to the overall CLL14 data to model the impact of the del(17p)/*TP53* mutation on efficacy outcomes, to maximise the predictive power of the available data. The covariate approach assumed proportional hazard rates between del(17p)/*TP53*-mutated and non-del(17p)/*TP53*-mutated populations, which the company demonstrated to be valid both statistically and based on a visual inspection. The company used the same extrapolation models as described above for the non-del(17p)/*TP53*-mutated population. For PFS, the company applied the base-case hazard ratio derived from the comparison with Mato (2018) to the VenG PFS curve for del(17p)/*TP53*-mutated patients to derive a PFS curve for ibrutinib. The same was done for the OS curve using the OS hazard ratio from the Mato (2018) comparison. In the same manner as the extrapolations for the population without a del(17p)/*TP53* mutation, the hazard rates were constrained by background mortality, and there could not be more patients in the PFS health state than there were alive in total. **The ERG** notes that by applying a del(17p)/*TP53* mutation covariate to the overall CLL14 data, the company includes patients who received GClb in their analysis. These patients are irrelevant and potentially misleading for the comparison to ibrutinib. The ERG also comments that the company provided no evidence to either support or refute an assumption of an interactive effect between the mutation and the treatment received. In addition, the ERG is unable to verify whether the assumption of proportionality between ibrutinib and VenG for PFS and OS holds due to the small sample size, and notes that it the assumption is violated all the comparisons presented by the company would be unreliable. The ERG also queries why the company chose to model OS differently for VenG and ibrutinib based on the HR derived from the indirect comparison, which is inconsistent with their approach for modelling OS for the non-del(17p)/*TP53*-mutated population, where the same curve was used for both VenG and GClb (see Issue 3). Finally, the ERG notes that in the Markov traces for VenG and

	ibrutinib, patients spend very little time in the post-progression health state, which it considers to be implausible (see Figure 4 and Figure 5). As both the PFS and OS extrapolations contribute to these traces the ERG investigated whether either could be considered more reliable, but clinical input suggests that both extrapolations are too optimistic. **Figure 4. Markov trace for VenG in del(17p)/*TP53*-mutated population**  Source: Figure 7, Final ERG report

Figure 5. Markov trace for ibrutinib in del(17p)/*TP53*-mutated population

Source: Figure 8, Final ERG report

As clinical input suggested the company's OS and PFS curves were implausible, the ERG investigated alternatives. The ERG found the 1-knot hazard spline model to most plausible because:

1. it produces 5-, 10- and 20-year PFS estimates closer to that predicted by the ERG's clinical expert than the company's base-case model (see Table 6 and Table 7), and
2. patients would receive later lines of therapy for a longer and more plausible duration than in the company's base-case model (years, rather than years).

Table 6. Comparison of PFS estimates between company's and ERG's base-case for patients with del(17p)/*TP53* mutation

Estimate	5 year	10 year	20 year
Company			
VenG (independent log-logistic extrapolation from CLL14)			
Ibrutinib (HR of 0.66 applied to VenG extrapolation)			

	ERG			
	VenG (independent 1-knot hazard spline)	[redacted]	[redacted]	[redacted]
	Ibrutinib (HR of 0.66 applied to VenG extrapolation)	[redacted]	[redacted]	[redacted]
	External reference			
	ERG clinical expert (same predictions for both treatments)	10%	0%	0%

Source: Adapted from Table 28, ERG Final report

Table 7. Comparison of OS estimates between company's and ERG's base-case for patients with a del(17p)/*TP53* mutation

Estimate	5 year	10 year	20 year
Company			
VenG (exponential dependent extrapolation from CLL14)	[redacted]	[redacted]	[redacted]
Ibrutinib (HR of 0.84 applied to VenG extrapolation)	[redacted]	[redacted]	[redacted]
ERG			
VenG (dependent 1-knot hazard spline)	[redacted]	[redacted]	[redacted]
Ibrutinib (HR of 0.84 applied to VenG extrapolation)	[redacted]	[redacted]	[redacted]
External reference			
ERG clinical expert (same predictions for both treatments)	40%	10%	0%

Source: Adapted from Table 28, ERG Final report

Why this issue is important	In the company's deterministic sensitivity analyses, the PFS and OS hazard ratios have a large impact on the ICER in the del(17p)/*TP53*-mutated patient population. In addition, changing the assumptions regarding the time-to-event parameters and extrapolations has a significant impact on the net monetary benefit (NMB) associated with VenG (see Table 8). The greater the NMB at a given willingness-to-pay threshold, the more cost-effective a treatment is relative to the comparator.

Table 8. Cost-effectiveness results comparison for the del(17p)/TP53-mutated population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB (WTP: £20k per QALY)	NMB (WTP: £30k per QALY)
Company's preferred base-case							
Ibrutinib	[redacted]	4.153				[redacted]	[redacted]
VenG	[redacted]	3.991	[redacted]	-0.163	[redacted]		
Results based on the ERG's change in time-to-event parameters and extrapolations							
Ibrutinib	[redacted]	3.690				[redacted]	[redacted]
VenG	[redacted]	3.451	[redacted]	-0.238	[redacted]		

Source: Table 53, ERG final report

* South west quadrant ICERs, which denote cost savings per QALY foregone.

Technical team preliminary judgement and rationale

The technical team agrees with the ERG that there are uncertainties regarding the company's methodology of applying a covariate to model the impact of the del(17p)/*TP53* mutation on outcomes, as irrelevant patients receiving GClb are included in the analysis.

The technical team acknowledges that the ERG's PFS extrapolation is closer to that estimated by their clinical expert than the company's extrapolation, but notes the extrapolations remain far above these estimations, particularly for ibrutinib. The technical team also notes that the ERG's clinical expert estimates that the PFS curves should be the same for both treatment arms, while the ERG applies the hazard ratio derived from the indirect comparison (see Issue 5).

The technical team considers that in the absence of extrapolations that more closely align with the estimations of the ERG's clinical expert, the ERG's extrapolations are more appropriate than those of the company.

Issue 7 – Pre-progression off-treatment utility

<table>
<tr><td>Questions for engagement</td><td>Which is the more plausible utility value for the ‘pre-progression off treatment’ health state: the company’s base-case value of 0.82 derived from the company’s submission for TA343, or the ERG’s re-calculated value of 0.77 based on the gender-weighted, age-specific value of the general population?</td></tr>
<tr><td>Background/description of issue</td><td>The company collected health-related quality of life (HRQoL) data as part of CLL14 using the EQ-5D-3L. Completion rates were very high over the course of the trial, remaining [redacted] in both treatment arms until Month 30. The estimated PFS utility values from CLL14 are shown in Table 9.

<u>Table 9. Summary of estimated PFS utility values from CLL14</u>
<table>
<tr><th>Model</th><th>Overall population</th><th>Del(17p)/TP53</th><th>Non-del(17p)/TP53</th></tr>
<tr><td>Model 1</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Model 2 (with time)</td><td>[redacted]</td><td>[redacted]*</td><td>[redacted]</td></tr>
</table>
Source: Table 5, Company response to Feb 20 clarification questions

For the overall population and the non-del(17p)/TP53-mutated population, the utility values based on the data from CLL14 could be estimated from Model 2, which considers time as a relevant variable and is more in line with the progressive nature of the disease. For the del(17p)/TP53-mutated population, the utility values could be estimated from Model 1. In a response to a clarification question from the ERG the company noted that the CLL14-derived utility scores for the post-progression state are subject to considerable uncertainty due to the small patient numbers that progressed during the trial period.

In a company-sponsored advisory board, experts considered the utility values estimated from the CLL14 data to be unfeasibly high for the previously untreated CLL population as they exceed those of the general population when matched by age (the utility values from the general population are as</td></tr>
</table>

follows: 70-year old female: 0.77, 70-year old male: 0.79). The company were advised to obtain PFS and PPS utility values from recently published data sources instead.

The company conducted a systematic literature review (SLR) to identify studies assessing the HRQoL of patients with previously untreated CLL. However, none of the 16 identified studies included a UK population and thus do not align with the NICE reference case. As such, the company used the utility values from TA343 (obinutuzumab with chlorambucil for untreated CLL) instead. These are shown in Table 10. The company amended its original analysis to include separate utility values within the pre-progression state depending on whether the patient is on or off treatment, with the same utility values applied regardless of treatment arm.

Table 10. Base-case utilities used in the economic model (from TA343)

Progression stage	Utility value
Pre-progression off treatment (company)	0.820
Pre-progression off treatment (ERG)	0.7703
Pre-progression oral treatment	0.710
Pre-progression IV treatment	0.670
Post-progression	0.600

Source: Adapted from Table 31, Addendum to company submission

The ERG notes that while a large proportion of CLL14 trial participants contributed HRQoL data overall, it agrees with the company that only a small proportion of these were in the post-progression state. As such, the post-progression utility values derived from CLL14 are subject to considerable uncertainty. Overall, the ERG agrees with the company's rationale for not using the utility values from CLL14.

However, the ERG notes that the utility values taken from TA343 were obtained from a study deemed to be of low quality by the ERG that undertook TA343. In particular, the TA343 ERG raised a concern that the utility value of 0.82 for the 'pre-progression off treatment' state (see Table 10) was higher than the age-adjusted utility value for the general population (0.76). As such, for the

	current appraisal the ERG would prefer to limit the utility value for this state to that of the gender-weighted, age-specific value for the general population. To calculate this upper utility bound, the ERG estimated the utility value for a 72-year-old member of the general population, adjusted based on the gender population split in the company's submission. This approach aligns with that used in TA343. The age of 72 years was calculated by the ERG on the basis that the first-line treatments in CLL14 were given for a fixed duration of 12 months, and the mean baseline age used in the economic model was 71 years (i.e. 72 years is equal to 71 years plus 1 year). The utility value derived by the ERG from this calculation is 0.7703, which is closer to that used in TA343 (0.76) than the value selected by the company (0.82).
Why this issue is important	To be able to assess the clinical- and cost-effectiveness of VenG, it is important to identify the most appropriate utility for the PPS off-treatment health state. In the company's deterministic sensitivity analyses the PPS utility has a large impact on the incremental QALYs for VenG versus GClb for the non-del(17p)/*TP53*-mutated patient population, with a lower bound of [redacted] QALYs, and an upper bound of [redacted] QALYs.
Technical team preliminary judgement and rationale	The technical team considers the ERG's re-calculated utility value of 0.77 to be the more clinically plausible of the 2 options, and agrees with the ERG that the value of 0.82 proposed by the company was previously rejected in TA343.

Issue 8 – Quality of life impact of venetoclax with obinutuzumab

Questions for engagement	Does the PFS benefit of VenG over GClb in previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation translate into improved patient quality of life?
Background/description of issue	3 patient-reported outcomes (PROs) were collected in CLL14: the MDASI-CLL, EORTC QLQ-C30 and EQ-5D-3L. As previously described in Issue 7, completion rates for all 3 questionnaires remained [redacted] until Month 30. PROs were first assessed during the first obinutuzumab infusion and are planned to be followed until the end of the study. No evidence of significant differences was reported between the VenG and GClb treatment arms across any of the PRO tools: • **EQ-5D-3L:** The proportion of patients experiencing no problems across the five health states was comparable between the VenG and GClb arms, though generally numerically superior in the VenG arm for Question 6 'your own health today' (see Figure 6). Patients in both arms reported a slight improvement in usual activities and anxiety/depression during treatment, with the improvement in anxiety or depression maintained post treatment. • **MDASI-CLL:** No evidence of a [redacted] between treatment arms was reported based on any of the MDASI scales. • **EORTC QLQ-C30:** [redacted] in the VenG arm and [redacted] in the GClb arm for global health status/QoL, although no evidence of a [redacted] between treatment arms was evident at any point during the trial. While [redacted] were observed in dyspnoea in the VenG arm during treatment at [redacted]

Figure 6. Change from baseline in EQ-5D-3L for 'your own health today' score

Source: Company appendices, Figure 16

The company considers that the safety results demonstrate VenG to be tolerable, with a safety profile consistent with the established safety profiles of venetoclax and obinutuzumab. Toxicity is predictable and manageable in the population studied.

The PRO results suggest that the combination of VenG did not adversely impact HRQoL in patients with previously untreated CLL, while providing a much deeper response and superior PFS.

The ERG considers it [redacted] that patients treated with VenG did not experience any improvements in HRQoL, given the PFS benefits observed with VenG.

[redacted]

In its response to the ERG, the company stated that the similarity in the PROs between treatment arms may be due to 2 reasons:

	1) VenG patients only receive treatment for 1 year, while the progression-free period is much longer, and 2) the CLL14 population was elderly and co-morbid, and these co-morbidities may have a larger bearing on patients' perception of quality of life than the impact of treatment.
Why this issue is important	While QALY decrements due to adverse events were applied in the company's model and considered robust by the ERG, it is important to understand whether the key claimed clinical benefit of VenG (extending PFS) has an impact on patient quality of life, particularly in the absence of any obvious OS benefit.
Technical team preliminary judgement and rationale	The utility values derived from CLL14 were considered unreliable (see Issue 7), and utilities derived from TA343 were incorporated into the economic model instead. The data from CLL14 [redacted], and therefore the technical team is concerned that applying the utility values from TA343 may overestimate the HRQoL impact of patients remaining progression free on VenG, and the associated QALYs. The ERG notes that if the per arm PFS and PPS utilities from CLL14 are applied to the economic model, the QALY difference between VenG and GClb in the non-del(17p)/*TP53*-mutated patient population is [redacted] compared to the base case. Incremental QALYs are 1.057 in the base case in favour of VenG, compared with 0.052 in the scenario with the CLL14 utilities applied.

4. Issues for information

Tables 11 to 14 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 11. VenG compared with GCIb in patients unsuitable for FCR/BR without del(17p)/*TP53* mutation (list prices)

		Net monetary benefit		Change from base case	
Alteration	**Technical team rationale**	**WTP: £20k/QALY**	**WTP: £30k/QALY**	**WTP: £20k/QALY**	**WTP: £30k/QALY**
Company base case	–	[redacted]	[redacted]	N/A	N/A
1. ERG-preferred PFS extrapolation	Technical team agreed with the ERG's amendment (see Issue 2)	[redacted]	[redacted]	[redacted]	[redacted]
2. ERG-preferred OS extrapolation	Technical team agreed with the ERG's amendment (see Issue 3)	[redacted]	[redacted]	[redacted]	[redacted]
3. ERG-preferred TTNT extrapolation	Technical team agreed with the ERG's amendment (see Issue 4)	[redacted]	[redacted]	[redacted]	[redacted]
4. ERG-preferred PFS, OS and TTNT extrapolations	Technical team agreed with the ERG's amendment (see Issues 2, 3 and 4)	[redacted]	[redacted]	[redacted]	[redacted]
5. ERG-preferred utility value for 'pre-progression off treatment' health state	Technical team agreed with the ERG's amendment (see Issue 7)	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness	–	[redacted]	[redacted]	[redacted]	[redacted]

		Net monetary benefit		Change from base case	
Alteration	**Technical team rationale**	**WTP: £20k/QALY**	**WTP: £30k/QALY**	**WTP: £20k/QALY**	**WTP: £30k/QALY**
estimate (both 4 and 5 above)					

Table 12. VenG compared with ibrutinib in patients with del(17p)/*TP53* mutation (list prices)

		Net monetary benefit		Change from base case	
Alteration	**Technical team rationale**	**WTP: £20k/QALY**	**WTP: £30k/QALY**	**WTP: £20k/QALY**	**WTP: £30k/QALY**
Company base case	–	[redacted]	[redacted]	N/A	N/A
1. Hazard ratios derived from the indirect comparison using the data from Ahn (2018)	Scenario analysis, given the uncertainty around the indirect comparison (see Issue 5)	[redacted]	[redacted]	[redacted]	[redacted]
2. Hazard ratios derived from the indirect comparison using the pooled ibrutinib data	Scenario analysis, given the uncertainty around the indirect comparison (see Issue 5)	[redacted]	[redacted]	[redacted]	[redacted]
3. Assumption of equal efficacy (PFS and OS) between VenG and ibrutinib	Scenario analysis, given the uncertainty around the indirect comparison (see Issue 5)	[redacted]	[redacted]	[redacted]	[redacted]
4. ERG-preferred PFS extrapolation	Technical team agreed with the ERG's amendment (see Issue 6)	[redacted]	[redacted]	[redacted]	[redacted]

		Net monetary benefit		Change from base case	
Alteration	**Technical team rationale**	**WTP: £20k/QALY**	**WTP: £30k/QALY**	**WTP: £20k/QALY**	**WTP: £30k/QALY**
5. ERG-preferred OS extrapolation	Technical team agreed with the ERG's amendment (see Issue 6)	[redacted]	[redacted]	[redacted]	[redacted]
6. ERG-preferred TTNT extrapolation	Technical team agreed with the ERG's amendment (see Issue 6)	[redacted]	[redacted]	[redacted]	[redacted]
7. ERG-preferred, PFS, OS and TTNT extrapolations	Technical team agreed with the ERG's amendment (see Issue 6)	[redacted]	[redacted]	[redacted]	[redacted]
8. ERG-preferred utility value for 'pre-progression off treatment' health state	Technical team agreed with the ERG's amendment (see Issue 7)	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate (both 7 and 8 above)	–	[redacted]	[redacted]	[redacted]	[redacted]

Table 13. Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Small patient numbers: clinical evidence for del(17p)/*TP53*-mutated patients based on a small subgroup from CLL14 trial	The clinical evidence for VenG in the subgroup of patients with del(17p)/*TP53* mutation is based on subgroup of 25 patients out of a total of 216 recruited in the VenG arm in CLL14. The small patient numbers create considerable uncertainty when assessing the relative efficacy of VenG in this patient subgroup.	Unknown
Double counting of patients and inclusion of non-subgroup patients within the evidence for a subgroup	The entire CLL14 patient population (including patients both with and without del(17p)/*TP53* mutation) was used to provide evidence for the subgroup without del(17p)/*TP53* mutation. The same applies for the subgroup with del(17p)/*TP53* mutation, where a covariate was applied to the entire CLL14 patient population to model the impact of the mutation. This population included patients receiving GClb, who would be irrelevant for the comparison with ibrutinib. As the del(17p)/*TP53*-mutated patients were included in the analysis for both subgroups, these patients are double-counted in the analysis.	Unknown
Immature evidence base	The OS data for CLL14 are immature. The median OS had not been reached in either treatment arm, and only [redacted] of the study population had died. Median PFS had not been reached in the VenG arm, and was 35.6 months in the GClb arm. The immaturity	Unknown

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	of the clinical data means that long-term extrapolations are associated with a high degree of uncertainty.	
Indirect treatment comparison with ibrutinib in del(17p)/*TP53*-mutated patients	No head-to-head data is available for the comparison with ibrutinib, and a naive indirect comparison was undertaken. The results of the indirect comparison are subject to a high degree of uncertainty due to small patient numbers in all included trials, and considerable heterogeneity between patient populations.	Unknown
Time-to-event extrapolations	As described in Issues 2, 3, 4 and 6, there is uncertainty regarding the most appropriate long-term extrapolations for the time-to-event endpoints, which will drive costs and QALYs in the cost-effectiveness model.	Unknown
Proportionality assessments	The assessment of proportional hazards is not always clearly reported by the company, and for some outcomes this assumption is likely to be violated (e.g. DoR, TTNT). Where this is the case, the hazard ratios derived by the company may not accurately capture the differences between treatment arms.	Unknown
Most plausible utility values	As described in Issue 7, there is some uncertainty as to the most plausible utility value for the 'pre-progression off treatment' health state, which impacts the cost-effectiveness estimates.	Unknown

Table 14. Other issues for information

Issue	Comments
Selective outcome reporting	The published protocol and NCT record lists ORR and MRD at the completion of combination treatment assessment as outcomes captured in CLL14, but these are not reported in the company submission. This introduces a risk of bias as a result.
Open-label design	There is a risk of performance bias and detection bias with an open-label trial, although overall the ERG considers CLL14 to be well designed and have a low risk of bias.
Deaths included as events in TTNT analysis	In the company submission deaths were included as TTNT events, rather than as censored observations. The ERG is unclear as to the extent to which this confounds the TTNT analysis, but considers it to be a potentially incorrect approach as the reader would understand a patient experiencing a TTNT event to have moved onto a subsequent line of therapy, when in fact they are no longer alive. In a subsequent analysis requested by the ERG where death events were censored, the company presented a hazard ratio of [redacted] in favour of VenG. This supports that VenG has a benefit on TTNT, although the company did not provide any information on clinical significance or confidence intervals.
Dose reduction and treatment alteration reporting	The reasons for and level of dose reductions or treatment alterations is not consistently reported for all treatments, and the ERG is uncertain as to the impact of such modifications.
Incorrect reporting of CLL14 data for (del)17p/*TP53*-mutated patients	The numbers, baseline characteristics and results of patients with del(17p)/*TP53* mutation in CLL14 reported in the company submission and CSR were incorrect. The company then failed to correct these in the updated indirect comparison.
Incorrect reporting of information from other studies in indirect comparison	The ERG notes several inaccuracies in the descriptions of the Mato (2018) and Ahn (2018) studies included in the indirect comparison, most notably regarding the sample sizes included in the analysis.
Differences between the (del)17p/*TP53*-mutated subgroups between the CSR and the economic model	The company used different algorithms between the CSR and economic model to determine the del(17p)/*TP53*-mutated patient subgroups. Although the rationale for this is not justified by the company, the ERG considers that it has little impact on the cost-effectiveness analysis.

Issue	Comments
Unit costs in economic model	Some discrepancies in the unit costs included in the economic model were identified by the ERG when comparing to a previous appraisal (TA561), but these are not expected to have a significant impact on incremental costs or ICERs.
Discrepancies between treatment arms in baseline comorbidities	The ERG identified some baseline imbalances between treatment arms in the following: vascular (specifically hypertension), respiratory, thoracic and mediastinal disorders (in particular COPD and asthma) and for psychiatric disorders (specifically insomnia). These were all more common in the VenG arm, which may increase the rate of infective AEs in this group.
Chlorambucil treatment duration	There is a discrepancy between the number of Clb cycles used in UK clinical practice when in combination with obinutuzumab (6 cycles) and the number of Clb cycles received in the comparator arm in CLL14 (12 cycles). The ERG agrees with the company that the overall Clb dose received in CLL14 is similar to that received in UK clinical practice, with overall dose a greater driver of efficacy than number of treatment cycles. The company considers that using a 6-cycle Clb treatment duration in CLL14 would appear biased towards VenG, and that assuming 12 cycles of GClb efficacy in the control arm makes the comparison more conservative for VenG. Applying the costs associated with 6 rather than 12 cycles of Clb while maintaining the efficacy associated with 12 cycles has little impact on the cost-effectiveness analysis.
Innovation	The company considers the drug to be innovative, a view supported by the ERG's clinical expert. However, the technical team considers that all relevant benefits associated with VenG are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company or the ERG. Patient and professional submissions highlight that restricting VenG to patients unsuitable for FCR or BR would deny younger 'fitter' patients access to a superior treatment that is better tolerated than existing options.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Thursday 2 July 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information

submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	AbbVie
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Questions for engagement

Issue 1: Patient population	
Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal?	In addition to the comparison of VenG to GClb in the FCR/BR ineligible patient population, a comparison of VenG to FCR/BR was requested by the ERG and technical team. A comparison of VenG with FCR and BR is provided as an Appendix to this response alongside the corresponding economic model version.
Is the patient population in the CLL14 trial appropriate for decision-making, particularly in the company's subgroup without a del(17p)/TP53 mutation?	The patient population in the CLL14 trial is appropriate for decision-making. The inclusion of UK sites and the fact the protocol was designed according to standard of care in the UK means that the trial results are generalisable to UK patients and therefore appropriate for decision making. Regardless of the number of UK patients enrolled in the CLL14 trial, clinical experts have commented that the CLL14 patient population is representative of the vast majority of patients with CLL being treated in the UK. Most patients in the CLL14 trial receiving subsequent lines of treatment were treated with targeted agents, suggesting that the treatment options available in recruiting countries were consistent with the UK treatment pathway. The technical report incorrectly states that "*the entire CLL14 trial population (which included patients with and without del(17p)/TP53 mutation) was used as evidence for the subpopulation without del(17p)/TP53 mutation*". 31 patients were included in the correlation coefficient for the modelled population with del(17p)/*TP53* mutation; all 31 were confirmed del(17p)/*TP53* mutation cases. 391 patients were included in the correlation coefficient for the modelled population without del(17p)/*TP53* mutation; 389 were with confirmed normal del(17p)/*TP53* mutation status and two were with missing del(17p) mutation status but had confirmed normal *TP53* mutation status. This is in line with the model algorithm for allocation of patients into those two populations, as described in Section B.3.2.1 of the original company submission (CS).

Issue 2: The most plausible PFS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which PFS extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	The company's base case extrapolation for PFS (log-logistic) is the most plausible selection for VenG and GClb in the patient population without del(17p)/*TP53* mutation. Nevertheless, please note that VenG remains dominant versus GClb in the non-del(17p)/*TP53* mutation population when the ERG's preferred PFS extrapolation is applied in the model. As described in Section B.3.3.6 of the original CS, the selection of the log-logistic model as the base case for PFS was based on clinician advice regarding UK clinical practice and in line with NICE DSU TSD14[1]. CLL14 projections were not expected to match those of CLL11, largely due to the differences in Clb cycles between the trials, and the fact that the projections made in the latter were not limited to patients without del(17p)/*TP53* mutation (6% of CLL11 participants had confirmed del(17p)/*TP53* mutation status).[2] As discussed further in response to Issue 3, CLL14 projections were not expected to completely match the ERIC study either, due to differences between the trials (baseline CIRS scores, the real-world evidence setting and no inclusion of UK centres) rather than the CLL14 extrapolations being overly optimistic. Spline models are particularly informative in the presence of a continuous plateau in observed data. In the case of CLL14, the mild flattening of the Kaplan–Meier (KM) curves towards 3.5 years cannot be considered a stable plateau and this shape is expected to change with longer follow-up, as demonstrated by the August 2019 data cut.[3] The KM curves are expected to naturally meet rates of general population mortality in the long-term due to an older, comorbid population. Therefore, given the data immaturity and KM shape, the spline models are not any more informative than standard parametric models. Differences between the ERG's and the company's preferred base case can be seen at three key timepoints (3-, 5- and 10-years): • It is important to note that observations from the CLL14 trial at 3 years, referenced in Table 1 of the technical report, are sourced directly from the CSR and based on data from the most recent data cut (August 2019; 39.6 months follow-up).[3] These figures include projections for the total trial population (including both undefined and confirmed del(17p)/*TP53* mutation cases) and are expected to be lower, on average, than projections using non-del(17p)/*TP53* mutation patients alone. In summary, model extrapolations for this timepoint should use KM data on non-del(17p)/*TP53* mutation patients only. KM data for PFS in the non-del(17p)/*TP53* mutation population only are

	included in the model ("KM data" sheet): [redacted] and [redacted] for the VenG and GClb arms, respectively. This means that the selected log-logistic base case is, in fact, [redacted] and [redacted] lower than the observed benefit, for VenG and GClb respectively, in this modelled population. The selected base case is aligned with the observed benefit from CLL14 at 3 years and is a slightly conservative estimate, rather than an overestimation of observed PFS benefit. • In the ERG's preferred approach, PFS is slightly below the CLL11 5-year projection (25%), whereas the company's selected base case is [redacted] higher and is aligned with the trend expected to result from different GClb dosing/cycles between the two trials, as well as differences in baseline risk. • The ERG's preferred base case at 10 years does not align with the views of three UK experts who unanimously confirmed that approximately 10% of their patients were in PFS at 10 years, and who all rejected models with projections closer to 0% for that timepoint. The ERG expert stated that, at 10 years, [redacted] of their patients will be in PFS, however, this is not aligned to the views of three UK experts on previously untreated patients with CLL without del(17p)/*TP53* mutation, who agreed with the original base case selection for PFS outcome (log-logistic distribution) and suggested that it is a better representation of UK clinical practice. It is important to note that both the ERG's and the company's preferred base case are aligned in terms of the timepoint at which PFS reaches background mortality (VenG at [redacted] years, GClb at [redacted] years). In eliciting expert clinical opinion on plausibility of long-term efficacy projections, we followed the approach to focus on landmarks where clinical experience is established (i.e. standard of care) and note that this is not necessarily the approach taken by the ERG.
Issue 3: The most plausible OS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which overall survival (OS) extrapolation model is most plausible for GClb in the patient population without del(17p)/*TP53* mutation?	The company's base case extrapolation for OS (exponential) is the most plausible selection for GClb in the patient population without del(17p)/*TP53* mutation. Nevertheless, please note that VenG remains dominant versus GClb in the non-del(17p)/*TP53* mutation population when the ERG's preferred OS extrapolation is applied in the model. CLL14 is the most robust source of evidence and should be used to inform OS projections and reimbursement decisions for a number of reasons including dosing, the baseline risk of participants and the changing treatment landscape of relapsed/refractory (R/R) CLL. For modelling purposes, CLL14 OS data should be used as the evidence base, with long-term OS projections informed by general population mortality, as per the model's partitioned survival

	analysis design. VenG is a more effective treatment in terms of PFS compared with GClb, making the approach whereby VenG and GClb are assumed to have an equal OS a conservative one. There are various issues with using ERIC as the basis for extrapolations: • Firstly, ERIC is a real-world evidence study and, as such, is less robust than the gold standard RCT design. • Secondly, the availability of VenR at relapse is not commented on in this manuscript and therefore might not be representative of the current pathway. Availability of VenR was limited for those patients progressing earlier in the study given that VenR was licensed in late 2018. • Thirdly, Clb dosage was lower in the ERIC study compared with CLL14, as a result of differences in the number of cycles (6 versus 12 for ERIC and CLL14, respectively) and the median relative dose intensity (75.1% versus 95.4% for ERIC and CLL14, respectively). • Lastly, given the absence of UK centres, it is unclear if the ERIC study can be considered representative of UK clinical practice which is potentially inadequately captured in the study protocol and facilitation. As a result, ERIC does not provide a good guide for the extrapolations, particularly in relation to OS outcomes. CLL14 is representative of current practice and offers higher quality data compared with retrospective real-world evidence studies, with outcomes which are at least as good, if not superior, to the available data with GClb combinations in similar patient populations. It is not surprising that CLL14 projections are not aligned with CLL11, since the latter does not adequately consider recent developments in treatments for patients with R/R CLL (VenR and ibrutinib).[2] However, it is worth noting that CLL11 is of higher quality than the ERIC study due to its RCT design. For clarification, the model does indeed account for increased risk of death, which was tested in scenario analyses ("Patient Distribution" sheet, cells R9 and R15). The ERG's clinical expert is correct that '*no evidence is available on the efficacy of subsequent treatments following first-line VenG*' as only [redacted] patients who were originally treated with VenG in the CLL14 trial received a subsequent line of

	treatment following disease progression, and therefore data on the efficacy of subsequent treatments, following VenG, are limited. However, there is increasing evidence of the efficacy of ibrutinib following venetoclax regimens in the R/R setting. High overall response rates, of up to 84%, and median PFS of 32 months, was observed in Bruton tyrosine kinase inhibitor (BTKi)-naïve patients in a RWE, multicentre, retrospective cohort study (CORE Registry/UK CLL Forum/US/EU Sites).[4] In addition, 100% of evaluable patients receiving ibrutinib after VenR in the MURANO study attained a response.[5] The outcomes reported in these studies confirm that patients achieve high response rates with ibrutinib following initial treatment with venetoclax regimens, reinforcing the efficacy of BTKis after venetoclax.
Issue 4: Subsequent treatment costs	
Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?	The company's approach to model subsequent treatment is considered the most suitable. Nevertheless, please note that when time on subsequent treatment is constraint by figures reported in the literature, as per the ERG's preferred approach, VenG remains cost-effective in both with and without del(17p)/*TP53* mutation populations. The current model version does not accommodate treatment sequencing in the R/R setting; the only reliable data available are on second line therapy, with only median values available, which is taken into account in calculations of average treatment cycle. Data on long-term use of R/R treatments are incomplete and not yet available, due to the timeframe that these innovations entered the treatment pathway (2011 and 2018 for ibrutinib and VenR, respectively).[6] Due to this lack of available data, a model design of treatment sequencing would be based solely on clinical opinion, leading to a more uncertain evidence base. Applying a 50:50 breakdown of the costs of the most frequently used R/R agents until end-of-life care generates a fair average cost for the time a patient spends in the post-progression survival (PPS) health state. In this way, the evidence gaps regarding published long-term use can be overcome in a clinically plausible way. The modelling position taken in the original CS will assist the committee in making firmer reimbursement decisions in terms of the introduction of VenG to the front-line setting of CLL. There is no published literature on time-to-next treatment (TTNT) per exact line of therapy in the R/R setting and therefore it was not possible to account for gaps between different treatment lines in the model. Instead, experts stated that patients who discontinue ibrutinib are likely to move on to VenR and vice versa. Therefore, applying a 50:50 ratio of those treatments across treatment arms, and modelling these continuously until end-of-life, is the only fair comparison to UK clinical practice.

	It is true that patients in the model spend more time on later lines of therapy in the GClb arm and that this is equal to the difference between the proportion of patients alive and the proportion of patients in the TTNT state, as per the partitioned survival analysis design. Therefore, it is likely that the relative difference between arms favours VenG with respect to PPS model calculations but this is driven by the difference in model traces between TTNT (that is closely correlated with PFS) and OS, rather than the costing approach itself. The modelling approach of subsequent treatment costs is applied equally to both arms in the comparison. Experts also confirmed there is increasing use of VenR in patients with R/R CLL. A scenario in which subsequent therapy was assumed to be 20% ibrutinib and 80% VenR was explored in the original CS and the Addendum (Scenario 4 of the subsequent treatment scenarios). In both submission documents, VenG demonstrated dominance over GClb (net monetary benefit: [redacted] and [redacted] versus [redacted] for the base case). To note, the information on interventions received as later lines of therapy has been misquoted in the technical report: "*the company provided information on the interventions received as later lines of therapy by patients in CLL14. The most common second-line treatment was ibrutinib, with a median treatment duration of* [redacted] *in patients receiving GClb as a first-line treatment, and* [redacted] *in patients receiving VenG as a first-line treatment.*" In response to clarification question A2 following the Addendum submission, these data were provided as the median ibrutinib treatment duration, but only for patients with del(17p)/*TP53* mutation. This is important because only four patients are accounted for in each arm for this treatment duration. When looking at the broader patient population, i.e. non-del(17)p/*TP53* mutation patients, the median treatment duration for ibrutinib should be [redacted] in patients receiving GClb as a first-line treatment (27 patients received ibrutinib) and [redacted] in patients receiving VenG as a first-line treatment (3 patients received ibrutinib). As requested, a revised version of the Addendum model has been provided where the time on subsequent treatment has been constrained by the literature-reported values (only median values available). The methodology used to calculate subsequent treatment costs in the new version of the model is described in the accompanying Appendix (Section A.3.1).

All results in the Addendum model remain the same except for the total subsequent treatment costs for VenG and GClb. Subsequently, the incremental costs and incremental cost per QALY are impacted.

Table 1 provides an overview of the results, for both the previous Addendum model version and the updated model version.

For the non-del(17p)/*TP53* mutation population, the total costs for both the VenG and GClb arms are reduced. For GClb the total cost has reduced by 36% and the incremental costs have reduced by 62%, compared with the previous model version. However, the direction of the incremental cost per QALY remains the same and VenG is still the dominant treatment option compared with GClb.

For the del(17p)/*TP53* mutation population, the cost of VenG has reduced marginally and the cost of ibrutinib remains the same.

Table 1: Comparison of results between previous and updated addendum models (list price)

Treatment	Addendum model (previous)			Addendum model (updated)		
	Total costs, £	Incremental costs, £	ICER, £/QALY	Total costs, £	Incremental costs, £	ICER, £/QALY
Non-del(17p)/*TP53* mutation population						
GClb	[redacted]			[redacted]	[redacted]	[redacted]
VenG	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Del(17p)/*TP53* mutation population						
Ibrutinib	[redacted]			[redacted]	[redacted]	[redacted]
VenG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the willingness-to-pay threshold.
Abbreviations: GClb: chlorambucil with obinutuzumab; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

	It is important to note that the ERG's suggested approach, where costs of R/R therapy are restricted to only one additional line of R/R therapy, is implausible as it does not align with UK CLL clinical practice. CLL is a chronic condition and the literature (which we acknowledge may not fully reflect the evolving treatment landscape) suggests that a proportion of patients receive several lines of treatment (at least 3).[7, 8] Nonetheless, even in this implausible scenario which unfavourably biases the VenG arm, its introduction as a treatment for patients with previously untreated CLL is still a cost-effective use of NHSE resources.
Which TTNT extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	The company's base case extrapolation for TTNT (log-logistic) is the most plausible selection for GClb in the patient population without del(17p)/*TP53* mutation. Nevertheless, please note that VenG remains dominant versus GClb in the non-del(17p)/*TP53* mutation population when the ERG's preferred TTNT extrapolation is applied in the model. The assumptions surrounding the distribution selected to fit the TTNT curve and extrapolate beyond the clinical trial period were primarily driven by external data (i.e. CLL11 trial)[2] and clinical opinion. The log-logistic distribution predicts an initial increase followed by a decreasing hazard over time, which might not be deemed a suitable distribution in oncology-specific survival analyses, where it can be expected that the risk of disease progression and death increase over time. Therefore, as stated in the NICE DSU TSD14,[1] the validity of the non-monotonic hazards should be considered when a log-logistic distribution is being selected. In the original CS, out of the parametric distributions, the Weibull and log-logistic distributions were both deemed potential candidates for the base case. However, the Weibull distribution was chosen based on external data and clinical opinion. This was chosen since it was the closest fit to the CLL11 5-year landmark TTNT data (i.e. at 5 years, 49% [95% confidence interval: 42, 55] of patients had not experienced a next treatment event). Secondly, the clinicians who were consulted at the time also stated that the Weibull distribution was a closer fit. Following the update of the survival analyses with the latest data (i.e. August 2019 data cut),[3] the parametric distribution fits were again compared with the external CLL11 data, where the log-logistic and Weibull distributions were still both close fits to the external data at 5 years. However, the clinicians consulted on the distribution selection suggested that the log-logistic distribution would be a better fit. When the point regarding 'decreasing hazards' was raised with the clinicians, they highlighted that "the longer a patient remains in remission, the less likely they are to require a subsequent line of therapy." As a result, making the initial increase in hazards followed by a monotonic decrease in

	hazards over time was applicable to how patients would move to the next line of treatment, therefore, giving rise to the discrepancy between the two submissions. Despite the ERG's approach being favourable in terms of the cost-effectiveness of VenG, the log-logistic distribution was considered the most plausible extrapolation by clinical experts. However, we acknowledge that the expert's projections fell between the lower (ERG base case) and upper (company base case) projections.
Issue 5: Indirect comparison hazard ratios: Del(17p)/*TP53*-mutated population	
Which PFS and OS hazard ratios are most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation?	The PFS and OS hazard ratios from the naïve indirect comparison with the Mato et al.[9] publication are the most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation. For all three sources of ibrutinib data identified,[9-11] the lack of participant characteristics makes it difficult to constructively evaluate whether VenG (in a comorbid, older population) is being compared with an equivalent ibrutinib cohort to allow for fair conclusions on relative efficacy of the two treatments. Data outputs from the naïve comparison further support the statement that it is difficult to quantify the exact benefit of introducing VenG in the del(17p)/*TP53* mutation population. As per model calculations, this appears to be a safe investment with the potential to substantially save NHSE resources. As suggested by the ERG, even if baseline characteristics were provided by the author, adjusted figures would not lead to firmer conclusions on the relative difference in efficacy between VenG and ibrutinib. It is anticipated that, if small sample sizes are further cut for adjustment purposes, then any matching-adjusted indirect comparison (MAIC) results would be no more informative regarding the relative efficacy trend of compared treatments. The sample size figures from the Ahn publication[10] are incorrectly referenced in the technical report (n=86). For clarity, analyses should use previously untreated patients with CLL with del(17p)/*TP53* mutation and treated with ibrutinib. For this purpose, the relevant subgroup sample size from the Ahn publication was 35 patients. The cohort referenced as n=51 includes patients with R/R CLL and does not include treatment-naïve patients only (n=35). Table 1 of the original study publication should clarify and confirm these statements.[10]

	Due to heterogeneity between CLL14 and ibrutinib sources, synthesising and combining data from the three sources is not necessary or appropriate. It is expected that larger numbers will narrow confidence intervals, but pooled estimates are misleading, and introduce greater heterogeneity in the comparison; instead, the Mato publication[9] should be used as the evidence base.
Issue 6: OS and PFS extrapolations: Del(17p)/*TP53*-mutated population	
Do you agree with the company's approach to modelling the OS and PFS curves for VenG and ibrutinib in patients with del(17p)/*TP53* mutation?	For the modelled del(17p)/*TP53* mutation population, there were no GClb patients included in the KM curves or estimation of HR as a relative difference of VenG to ibrutinib. These results were based on confirmed del(17p)/*TP53* mutation cases from the VenG arm of the CLL14 trial (n=25) and data on ibrutinib that were available from the literature. Some del(17p)/*TP53* mutation information from the GClb arm was indeed used to inform cost-effectiveness modelling in order to optimally account for the impact that the del(17p)/*TP53* mutation variable has on key modelled outcomes (i.e. PFS, OS). This approach aimed to increase the predictive power of the available data by including del(17p)/*TP53* as a covariate when conducting the time-to-event modelling. The outcome of those analyses was an estimated coefficient of how del(17p)/*TP53* mutation status impacts the rate or scale parameter of the parametric distributions which use an accelerated failure time model approach to generate the OS and PFS curves. A scenario of HR=1 was presented in the original CS and is permitted by model design. It was decided that this should not be used as the base case, for a more conservative approach, given the limited evidence available. We would like to clarify that Markov traces for this modelled population are aligned with clinical expectation post relapse from front-line CLL therapy. Specifically, in the model, the fact that patients spend very little time in the post-progression health state is consistent with the prognoses of this patient group and solely driven by extrapolated outcomes. These drive time spent in each health state as per the non-del(17p)/*TP53* mutation population. Projections were presented to 7 UK clinical experts and there was consensus that the projection of 10% PFS at 5-years (stated by ERG's clinical expert) was pessimistic. They all mentioned that it is difficult to compare projections with published literature due to lack of long-term use of ibrutinib. However, all agreed that a reasonable range for PFS at 5-years would be 30–60%, which aligns with both the ERG and the company base case. We therefore believe that the company base case is reflective of clinical practice.

	The UK clinical experts also consider 5-year OS projections for ibrutinib to be higher than the 10% projections reported by the ERG clinical expert and estimated this to be 20% (which is more closely aligned with the ERG and the company base case).
Issue 7: Pre-progression off-treatment utility	
Which is the more plausible utility value for the 'pre-progression off treatment' health state: the company's base-case value of 0.82 derived from the company's submission for TA343, or the ERG's re-calculated value of 0.77 based on the gender-weighted, age-specific value of the general population?	As discussed in the original CS and as agreed by the ERG, the CLL14 trial utility data are not suitable for the model's base case as the values are unrealistically high. Therefore, values and approaches used to inform past CLL submissions, that have faced the same data challenges, are the most appropriate input for the PFS off-treatment utility value: that of the general population (0.7703).
Issue 8: Quality of life impact of venetoclax with Obinutuzumab	
Does the PFS benefit of VenG over GClb in previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation translate into improved patient quality of life?	The ERG acknowledges the high utility values reported across both arms of the CLL14 trial and questions why there is no significant difference in CLL14 trial patient reported outcomes between VenG and GClb treatment arms, despite the large PFS benefit experienced by patients in the VenG arm relative to the GClb arm. The question is clarified as follows: • No differences in patient-reported outcomes were seen between treatment arms and therefore it is reasonable to assume that CLL14 PFS summarised values are indeed related to progression-free status of patients rather than administered treatment.

	• Moreover, as described in the original CS, the safety profile associated with VenG therapy is consistent with the established safety profiles of venetoclax and obinutuzumab, both of which have been extensively used in the NHS over the last few years (venetoclax as monotherapy and in combination with rituximab; obinutuzumab as monotherapy and in combination with other agents). All those considerations reinforce the argument that it is reasonable not to expect differences in utility values between arms due to administered therapy. • Finally, as suggested by the ERG and technical team, CLL14 utility values are not suitable for decision making due to limitations associated with mean values and bias of responses due to frailty, mentioned in points 1 and 2 of the technical report. Overall, VenG improves efficacy outcomes without compromising quality of life. Any corresponding toxicity is, in fact, tolerable and cannot be associated with substantially lower utility values compared with GClb. If there were substantial issues associated with VenG toxicity then this would have been reflected in CLL14 mean utility values, which would have never exceeded that of general population health in this instance.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

Appendix to

Company Technical Engagement Response

July 2020

File name	Version	Contains confidential information	Date
NICE VenG for CLL Appendix	Final	Yes	2nd July 2020

Contents

Tables

Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
BR	Bendamustine with rituximab
CI	Confidence Interval
CLL	Chronic lymphocytic leukaemia
Cri	Credible interval
ERG	Evidence Review Group
FCR	Fludarabine, cyclophosphamide and rituximab
GClb	Chlorambucil with obinutuzumab
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IV	Intravenous
LYG	Life years gained
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression-free survival
PPS	Post-progression survival
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SAE	Serious adverse event
TTNT	Time to next treatment
VenG	Venetoclax with obinutuzumab
WTP	Willingness-to-pay

A.1 Clinical effectiveness vs FCR/BR

A.1.1 *Background*

The primary objective for this analysis was to estimate the comparative effectiveness of venetoclax plus obinutuzumab (VenG) in FCR/BR eligible patients with previously untreated CLL with respect to PFS and OS. The efficacy of bendamustine with rituximab (BR) and fludarabine, cyclophosphamide and rituximab (FCR) was compared with VenG.

Patients with previously untreated chronic lymphocytic leukaemia (CLL) aged below 65 years with comorbidities not deemed clinically significant based on a cumulative illness rating scale (CIRS) score of less than 6 were considered as being 'fit'. Patients with previously untreated CLL who are 65 years of age or older and have clinically significant comorbidities (based on a CIRS score of 6 or higher) were considered as 'unfit'. Patients who were eligible to receive fludarabine and bendamustine-based therapy were also determined to belong to the 'fit' category for the purposes of this analysis.

A.1.2 *Data sources*

Clinical data for comparators were taken from published literature, identified from the clinical systematic literature review (SLR) presented in the original company submission (Appendix D). The SLR identified 36 RCTs, for which results were reported in 56 related publications.

An overview of the randomised-controlled trials (RCTs) that were used in the indirect treatment comparison (ITC), and reasons for including or excluding related publications is provided in Table 1.

Table 1: Overview of available evidence for the ITC

Trial	Publications used in the NMA	Additional publications, retrieved from the clinical SLR	Reasons for not using these additional publications
CLL14	Data on file (August 2019 data cut)[1]	Fischer, 2019. Venetoclax and Obinutuzumab in patients with CLL and coexisting conditions. *The New England Journal of Medicine.*	Same HRs reported as based on data on file (August 2018 data cut).
		Fischer, 2019. Effect of fixed-duration Venetoclax plus Obinutuzumab (VenG) on progression-free survival (PFS), and rates and duration of minimal residual disease negativity (MRD–) in previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) and comorbidities. *ASCO conference abstract.*	Unclear whether estimates for PFS are INV-assessed or IRC-assessed.
		Fischer, 2019. Fixed-duration Venetoclax plus Obinutuzumab improves progression-free survival and minimal residual disease negativity in patients with previously untreated CLL and comorbidities. *EHA conference abstract.*	Same HRs reported as based on data on file (August 2018 data cut).
		Tausch, 2019. Genetic markers and outcome in the CLL14 trial of the CGLLSG comparing front line Obinutuzumab plus Chlorambucil or Venetoclax in patients with comorbidity. *EHA conference abstract.*	Reports on CLL14 results for subgroup with del17p mutation.
		Al-Sawaf, 2019. High efficacy of Venetoclax plus Obinutuzumab in patients with complex karyotype (CKT) and chronic lymphocytic leukemia (CLL): a prospective analysis from the CLL14 trial. *EHA conference abstract.*	Reports on results for CKT, defined as presence of ≥3 chromosomal aberrations, subgroups.
COMPLEMENT1	Hillmen, et al. (2015)[2] Hillmen, et al. (2016)[3]	Offner, 2019. Long-term follow-up of previously untreated patients (pts) with chronic lymphocytic leukemia (CLL) treated with ofatumumab (OFA) and chlorambucil (CHL): Final analysis of the phase 3 COMPLEMENT 1 trial. *ASCO Conference abstract.*	The length of follow-up in the Hillmen et al. 2015 paper for OS and PFS was aligned with the CLL14 updated trial follow-up period for OS and PFS. To keep the follow-up duration between OS and PFS aligned, the OS and/or PFS HR were not updated based on the Offner publication.
iLLUMINATE	Moreno, et al. (2019)[4]	No additional evidence retrieved from the SLR.	N/A

	Moreno, et al. (2019)[5]		
Resonate-2	Burger, et al. (2018)[6] Barr, et al. (2018)[7] plus Tedeschi (2019) iwCLL2019 oral presentation (estimates of PFS and OS were used in the NMA)	Tedeschi, 2019. Five-year follow-up of patients receiving Ibrutinib for first-line treatment of chronic lymphocytic leukemia. *EHA conference abstract.*	Longer follow-up but not reported whether PFS was INV-assessed or IRC-assessed.
		Burger, J. A. et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 373, 2425-2437, doi:10.1056/NEJMoa1509388 (2015).	Original trial publication, longer follow-up available and presented in Barr, et al. (2018) and Tedeschi (2019).
		Burger, 2018. Ibrutinib for first-line treatment of older patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL): A 4-year experience from the Resonate-2 study. *EHA conference abstract.*	Updated PFS outcome only. To keep the follow-up duration between OS and PFS aligned, the PFS HR was not updated based on the Burger publication.
		Coutre, S. et al. Survival adjusting for crossover: phase 3 study of ibrutinib vs. chlorambucil in older patients with untreated chronic lymphocytic leukemia/small lymphocytic lymphoma. Haematologica 103, e249-e251, doi:10.3324/haematol.2017.175380 (2018).	Additional cross-over analysis. Longer follow-up available and presented in Barr, et al. (2018) and Tedeschi (2019).
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ALLIANCE	Woyach, et al. (2018)[8]	No additional evidence retrieved from the SLR	N/A
MaBLe	Michallet, et al. (2018)[9]	No additional evidence retrieved from the SLR	N/A

CLL11	Goede, et al. (2015)[10]	Goede, 2018. Overall survival benefit of Obinutuzumab over Rituximab when combined with Chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: Final survival analysis of the CLL11 study. *EHA conference abstract.*	The EHA abstract provides updated HRs for PFS and OS, but not for all treatment arms of the study.
		Goede, V. et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 370, 1101-1110, doi:10.1056/NEJMoa1313984 (2014).	
CLL10†	Eichhorst, et al.2016[11]	Eichhorst, 2016. Favorable Toxicity Profile and Long-Term Outcome of Elderly, but Physically Fit CLL Patients (pts) Receiving First Line Bendamustine and Rituximab (BR) Frontline Chemoimmunotherapy in Comparison to Fludarabine, Cyclophosphamide, and Rituximab (FCR) in Advanced Chronic Lymphocytic Leukemia (CLL): Update Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study). *ASH conference abstract.*	The full publication was used instead of the conference abstract to have more details on the results
ECOG†	Shanafelt, et al. 2018[12]	*No additional evidence retrieved from the SLR*	N/A

† The trials included only fit patients.
Abbreviations: CKT: complex karyotype; EHA: European Hematology Association; HR: hazard ratio; INV: investigator; IRC: Independent Review Committee; ITC: indirect treatment comparison; N/A: not applicable; NMA: network meta-analysis; OS: overall survival; PFS: progression-free survival; RWE: real-world evidence; SLR: systematic literature review.

A.1.2.1 Comparator data extraction

Individual patient level data and censoring times were estimated from published overall survival (OS) Kaplan–Meier (KM) curves for the Alliance trial, as the hazard ratio for OS was not reported in this trial publication.[8] The available KM curves were digitised using WebPlotDigitizer[13] to simulate patient level data from the Alliance trial using the methodology outlined by Guyot, et al.[14] This algorithm creates a simulated cohort of patients whose collective survival event and censored times are mathematically closest to the published KM data. For example, if a study reported KM data from 200 patients, this algorithm generates 200 simulated data points, each with a time to survival/progression event or time of censoring. The simulated patient level data were used to estimate the hazard ratio (HR) for OS using the *survival package in R*.[15]

The HRs estimated from the digitisation of KM curves for the Alliance trial were used in the NMA.

A.1.2.2 Defining fit versus unfit

Fitness of patients was identified as an important prognostic factor and effect modifier. Thus, to ensure the comparability of evidence, the trials included in the network were categorised as having 'fit' or 'unfit' patients. The classification of patients in the trials of interest as 'fit' or 'unfit' was based on criteria derived from the National Comprehensive Cancer Network (NCCN) guidelines as well as clinical significance as determined by clinical experts at an AbbVie-organised Advisory Board.[16] These criteria are presented in Table 2, with the classification of the trials included in the network presented in

Table 3.

Table 2: Criteria for categorising patients as fit or unfit based on trial inclusion criteria

Category	Definition
Fit patients	Patients aged <65 years, with CIRS score <6
	Fludarabine eligible patients
Unfit patients	Patients aged ≥65 years
	Patients aged <65 years with CIRS score ≥6
	Patients that are specified to be fludarabine ineligible

Abbreviations: CIRS: cumulative illness rating scale.

Table 3: Classification of trials included in the network as fit or unfit

Trial name	Comparators	Age, years		CIRS score ≥6	Fludarabine eligibility status	Fitness category
		<65	≥65			
CLL14	VenG	+	+	+	N/A	Unfit
	GClb					
CLL11	Clb	+	+	+	N/A	Unfit
	RClb					
	GClb					
MaBLe	BR	+	+	NR	+	Unfit
	RClb					
CLL10	BR	+	+	−	NR	Fit
	FCR					
Resonate-2	IBR	-	+	NR	NR	Unfit
	Clb					
iLLUMINATE	IBR+G	+	+	+	NR	Unfit
	GClb					
COMPLEMENT1	OClb	+	+	NR	+	Unfit
	Clb					
ECOG	IBR+R	+	+	NR	−	Fit
	FCR					
Alliance	BR	−	+	NR	NR	Unfit
	IBR+R					
	IBR					

Abbreviations: BR: bendamustine plus rituximab; CIRS: cumulative illness rating scale; Clb: chlorambucil monotherapy; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil plus obinutuzumab; IBR: ibrutinib monotherapy; IBR+G: ibrutinib plus obinutuzumab; IBR+R: ibrutinib plus rituximab; N/A: not applicable; NR: not reported; OClb: chlorambucil plus ofatumumab; RClb: chlorambucil plus rituximab; VenG: venetoclax plus obinutuzumab.
Source: Clinical trials.gov.

A.1.2.3 Input data for the NMA

Table 4 and Table 5 present the input information from the available publications, for PFS and OS respectively. This information was used in the network meta-analysis however only trials that contributed to the FCR and BR comparator data were incorporated in the calculation of HRs. For clarity, these sources are highlighted in **bold** throughout this report.

The resulting HRs from the NMA with blended fitness status were compared to VenG data from CLL14 that recruited unfit patients. For the purposes of these analyses, data from the entire VenG arm was used (to include del(17p)/*TP53* mutation positive cases and those with undefined status) (n=216) to align with populations studied in comparator trials. Including the del(17p) patients in the VenG arm is a conservative approach in comparing VenG with data from various literature sources aiming to optimally represent all 1st line CLL populations.

Table 4: Inputs for the NMA for PFS

Trial name	Assessment IRC/INV	Cox model	Intervention	Comparator	HR	95%CI lower bound	95% CI upper bound	p-value
COMPLEMENT1 (Hillmen, et al. 2015[2])	IRC	Stratified*	OClb	Clb	0.570	0.450	0.720	<0.0001
iLLUMINATE (Moreno, et al. 2019[4])	INV	Unstratified	IBR+G	GClb	0.260	0.160	0.420	<0.0001
Resonate-2 (Barr, et al. 2018[7])	IRC	Stratified*	IBR	Clb	0.121	0.074	0.198	<0.0001
Resonate-2 (Tedeschi et al, iwCLL2019)	IRC	Stratified*	IBR	Clb	0.146	0.098	0.218	NR
Alliance (Woyach, et al. 2018[8])	**IRC**	**Unstratified**	**IBR**	**BR**	**0.370**	**0.250**	**0.560**	**<0.001**
	IRC	**Unstratified**	**IBR+R**	**BR**	**0.400**	**0.270**	**0.600**	**<0.001**
MaBLe (Michallet, et al. 2018[9])	**IRC or INV**	**Stratified***	**BR**	**RClb**	**0.523**	**0.339**	**0.806**	**0.0030**
CLL11 (Goede, et al. 2015[10])	INV	Stratified*	GClb	RClb	0.400	0.330	0.500	<0.0010
	INV	Stratified*	GClb	Clb	0.180	0.140	0.240	<0.0001
	INV	Stratified*	RClb	Clb	0.440	0.340	0.560	<0.0001

CLL10 (Eichhorst, et al.2016[11])	**IRC or INV**	**Unstratified**	**BR**	**FCR**	**1.626**	**1.244**	**2.125**	**0.0003**
ECOG (Shanafelt, et al. 2018[12])	**NR**	**Stratified e**	**IBR+R**	**FCR**	**0.352**	**0.223**	**0.558**	**<0.0001**

*Adjusted hazard ratios were presented.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; Clb: chlorambucil monotherapy; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil plus obinutuzumab; HR: hazard ratio; IBR: ibrutinib monotherapy; IBR+G: ibrutinib plus obinutuzumab; IBR+R: ibrutinib plus rituximab; INV: investigator-assessed; IRC: Independent Review Committee-assessed; N/A: not applicable; NMA: network meta-analysis; NR: not reported; OClb: chlorambucil plus ofatumumab; PFS: progression-free survival; RClb: chlorambucil plus rituximab.

Table 5: Inputs for the NMA for OS

Trial name	Cox model	Intervention	Comparator	HR	95%CI lower bound	95% CI upper bound	p-value
COMPLEMENT1 (Hillmen, et al. 2015[2])	Unstratified	OClb	Clb	0.910	0.570	1.430	0.666
iLLUMINATE (Moreno, et al. 2019[4])	NR	IBR+G	GClb	0.921	0.479	1.772	0.810
Resonate-2 (Barr, et al. 2018[7])	Stratified*	IBR	Clb	0.432	0.210	0.860	0.015
Resonate-2 (Tedeschi et al, iwCLL2019)	Stratified*	IBR	Clb	0.450	0.266	0.761	NR
Alliance ‡ (Woyach, et al. 2018[8])	**Unstratified**	**IBR**	**BR**	**1.115**	**0.610**	**2.030**	**0.720**
	Unstratified	**IBR+R**	**BR**	**1.072**	**0.580**	**1.960**	**0.820**
MaBLe (Michallet, et al. 2018[9])	**Stratified***	**BR**	**RClb**	**0.975**	**0.505**	**1.880**	**0.939**
CLL11 (Goede, et al. 2015[10])	Stratified*	GClb	RClb	0.700	0.470	1.020	0.063
	Stratified*	GClb	Clb	0.470	0.290	0.760	0.0001
	Stratified*	RClb	Clb	0.600	0.380	0.940	0.024
CLL10	**Unstratified**	**FCR**	**BR**	**1.034**	**0.620**	**1.724**	**0.897**

(Eichhorst, et al.2016[11])							
ECOG (Shanafelt, et al. 2018[12])	**Stratified***	**IBR+R**	**FCR**	**0.168**	**0.053**	**0.538**	**<0.0001**

* Adjusted hazard ratios presented
‡ The HR (± 95% CI) were estimated based on digitised Kaplan–Meier curves from Woyach, et al. 2018.
Abbreviations: BR: bendamustine plus rituximab; CI: confidence interval; Clb: chlorambucil monotherapy; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil plus obinutuzumab; HR: hazard ratio; IBR: ibrutinib monotherapy; IBR+G: ibrutinib plus obinutuzumab; IBR+R: ibrutinib plus rituximab; INV: investigator-assessed; IRC: Independent Review Committee-assessed; N/A: not applicable; NMA: network meta-analysis; NR: not reported; OClb: chlorambucil plus ofatumumab; OS: overall survival; RClb: chlorambucil plus rituximab.

A.1.3 *Statistical methods*

The methodology is a Bayesian network meta-analysis (NMA) model, which preserves the randomisation of each trial. The outcome variables of interest are the hazard ratio (HR) of overall survival (OS) and the HR of progression free survival (PFS) of various treatments for patients with previously untreated CLL versus VenG. The comparators of interest for this decision problem are BR and FCR. The generalised linear model for treatment difference from Dias et al.[17] is a natural choice for these outcome variables. This study compares the difference in log hazard rates from various comparators, which results in the estimates of log hazard ratios (log HRs).

The NMA was conducted in a Bayesian framework, which makes the selection of priors important. Within this study, a non-informative prior was employed. For the treatment effect (log hazard ratio) a normal distribution with mean 0 and precision 0.0001 was used. Consequently, the prior treats all treatments equal and the difference in the estimated treatment effect comes predominantly from observed data. The use of non-informative priors is recommended by Dias et al.[17] Use of informative priors may be an alternative to non-informative priors, but this approach requires informed prior knowledge, which was unavailable in the context of these analyses in previously untreated CLL.

In the Monte Carlo simulation, three simulation chains were used with 60,000 iterations, 20,000 burn-ins and 1 thinning simulation chains. The Gelman-Rubin statistics, the size of the Monte Carlo error, auto-correlation function (ACF), trace plots and Kernel density plots were checked to assess the convergence. All analyses converged.

A.1.3.1 Fixed-effects and random-effects models

This analysis considers the fixed-effects meta-analysis. A random-effects model has not been used since each arm of the network is formed by only one trial. The primary difference between these methods is explained below, for more details please refer to Hoaglin et al.[18]

A fixed-effects model, for a simplified case of two treatment arms, comparing treatment A and treatment B, can be expressed in the following equations.

$$\eta_{jk} = \begin{cases} \mu_j, & k = A \\ \mu_j + d, & k = B \end{cases}$$

η_{jk} is the underlying outcome for treatment k in study j, μ_j the outcome for treatment A in study j and d the effect of treatment B relative to treatment A. The treatment effect, d, is assumed to be equal for all studies. On the other hand, the treatment effect differs by trial in the random-effects model. The treatment effect is typically assumed to be normally distributed with a certain mean and variance.

$$\eta_{jk} = \begin{cases} \mu_j, & k = A \\ \mu_j + \delta, & k = B \end{cases}$$

$$\delta \sim \mathcal{N}(d, \sigma^2)$$

The fixed-effects model was calculated in WinBUGS.[19]

For the Alliance trial, an adjustment was made to account for the correlation between treatment relative effects from the same trials. The correction was implemented using a vector of random effects for each trial, calculated using the distribution of one treatment effect conditional on the one of the other treatment effects from the same trial, therefore taking between-arm correlation into account. This approach, based on a conditional distribution formulation of the multivariate normal distribution, is proposed by Woods et al. and recommended by Dias et al.[17]

The autocorrelation between two hazard-ratios was defined as:

$$se_{k_1k_2} = \sqrt{\frac{(se_{k_1b}^2 + se_{k_2b}^2)(\frac{1}{n_{k_1}} + \frac{1}{n_{k_2}})}{(\frac{1}{n_{k_1}} + \frac{1}{n_{k_2}} + \frac{2}{n_b})}}$$

By transitivity, the standard error of the control arm (used as correction factor in the model) could therefore be defined as:

$$se_b = \sqrt{\frac{se_{k_1b}^2 + se_{k_2b}^2 - se_{k_1k_2}^2}{2}}$$

A.1.3.2 Outputs

The outputs included the mean, standard deviation, median and 95% CrI for the treatment difference, expressed as HRs, comparing any two treatments (pairwise) in the network in terms of PFS and OS, respectively.

A.1.4 *Data preparation*

This subsection describes the transformation of the observed data in Table 4 and Table 5 to an appropriate format for conducting an NMA. Dias et al. proposed a generalised linear model to analyse treatment difference, which is a natural choice to analyse the data.[17] It uses an identity link and treats log HR as a normally distributed continuous variable. See Dias et al. for the details of the statistical model and programming codes.[17]

The natural logarithm was applied to the HRs in Table 4 and Table 5. HR takes a value on the range $(0, \infty)$ and is not normal distributed. This is a violation on the assumption of program 7 in Dias et al.[17] Taking the natural logarithm of the HR mitigates this problem. To calculate the standard error, the natural logarithm was applied to the CI of the HRs first, and then a formula to transform CI to standard error was applied (see Higgins and Green[20] for further details): $se = (CI_{right} - CI_{left})/3.92$. This formula assumes that the transformed variable is normal distributed.

For the Alliance trial (Woyach et al. 2018[8]) individual patient level data was simulated from the Kaplan–Meier curves using the method proposed by Guyot et al,[14] since the HRs were not reported in the publication. The Cox regression was applied to each pair of the three arms to estimate the HRs and the corresponding 95% CIs. The HRs and the CIs were transformed to log hazards using

the methods by Higgins and Green.[20] The variance of the baseline treatment in the trial was calculated following the approach outlined in Section A.1.3.1.

A.1.5 *Results of the NMA*

The trials identified by the SLR could be connected into one network which is presented in Figure 1 and is utilised in the NMA. The initial NMA was performed considering all licensed treatments for previously untreated CLL; not all these treatments are reimbursed by NICE or of relevance for this appraisal. As such, there are more trials included in this network than only the ones that make the link between VenG vs. BR and VenG vs. FCR and those trials contributed to the final estimate of the relative efficacy.

Figure 1: Overall network of trials included in the NMA

Note that the NMA was performed broadly for previously untreated CLL patients therefore comparators not of interest for this submission were included in the network.
Abbreviations: BR: bendamustine with rituximab; Clb: chlorambucil monotherapy; FCR: fludarabine with cyclophosphamide and rituximab; GClb: chlorambucil with obinutuzumab; IBR: ibrutinib monotherapy; IBR+G: ibrutinib with obinutuzumab; IBR+R: ibrutinib with rituximab; MRD: minimal residual disease; NMA: network meta-analysis; OClb: chlorambucil with ofatumumab; RClb: chlorambucil with rituximab; VenG: venetoclax with obinutuzumab.

The NMA was conducted in a Bayesian framework and therefore there is no reporting of confidence intervals and p-values, as would be expected with a frequentist approach. Alternatively, the output of the NMA includes a credibility interval which can be interpreted like a confidence interval. If the null value of the hazard ratio (=1) falls within the credibility interval, the results can be interpreted as undecisive. If the null value falls *not* within the credibility interval, the corresponding hazard ratio

provides an indication of better (HR above 1) or worse (HR below 1) performance of the intervention versus the comparator.

A.1.5.1 Progression-free survival

The transformed PFS data used in the NMA are presented in Table 6.

Table 6: Progression free survival data for the network

Trial name	Tx1	Tx2	Tx3	Treatment comparison Tx1 – Tx2		Treatment comparison Tx2 – Tx3		Arms	Baseline variance
				log HR	SE	log HR	SE		
CLL14	GClb	VenG		−1.220	0.181			2	
CLL10	FCR	BR		0.486	0.137			2	
MaBLe	RClb	BR		−0.648	0.221			2	
iLLUMINATE	GClb	GIbr		−1.347	0.248			2	
Resonate-2	Clb	IBR		−1.924	0.203			2	
ECOG	FCR	IBR+R		−1.044	0.233			2	
COMPLEMENT1	Clb	OClb		−0.562	0.121			2	
Alliance	BR	IBR	IBR+R	−0.994	0.200	−0.916	0.201	3	0.011
CLL11	Clb	GClb	RClb	−1.715	0.128	−0.821	0.132	3	0.012

Abbreviations: BR: bendamustine plus rituximab; Clb: chlorambucil monotherapy; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil plus obinutuzumab; HR: hazard ratio; IBR: ibrutinib monotherapy; IBR+G: ibrutinib plus obinutuzumab; IBR+R: ibrutinib plus rituximab; OClb: chlorambucil plus ofatumumab; RClb: chlorambucil plus rituximab; SE: standard error; Tx: treatment.

Error! Not a valid bookmark self-reference. shows the meta-analysis results on the hazard ratio of PFS in the overall network. In Figure 2, the hazard ratio and the 95% credible intervals are presented visually. VenG shows numerically better efficacy than all comparators. Results of the pairwise comparison of treatments can be found in Table 8.

Table 7: NMA results for PFS

Treatment	HR	CrI 2.5%	CrI 97.5%
VenG (reference)			
FCR	3.873*	2.081	6.613
BR	5.607*	3.201	9.186

*Numerical finding.
Abbreviations: BR: bendamustine with rituximab; CrI: credible interval; FCR: fludarabine, cyclophosphamide and rituximab; HR: hazard ratio; NMA: network meta-analysis; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 2: Hazard ratios and 95% credibility intervals for the NMA of PFS

HRs above 1 should be interpreted as VenG having better efficacy than the comparator, HRs below 1 should be interpreted as giving preference to the comparator.
Abbreviations: BR: bendamustine plus rituximab; FCR: fludarabine, cyclophosphamide and rituximab; NMA: network meta-analysis; PFS: progression-free survival.

Table 8: Pairwise hazard ratios with 95% credibility intervals for the NMA of PFS

	VenG	FCR	BR
VenG	1	3.8730 (2.0810, 6.6130)	5.6070 (3.2010, 9.1860)
FCR		1	1.4697 (1.1420, 1.8600)
BR			1

Abbreviations: BR: bendamustine plus rituximab; FCR: fludarabine, cyclophosphamide and rituximab; NMA: network meta-analysis; PFS: progression-free survival; VenG: venetoclax plus obinutuzumab.

A.1.5.2 Overall survival

The transformed OS data used in the NMA are presented in Table 9.

Table 9: Overall survival data for the network

Trial name	Tx1	Tx2	Tx3	Treatment comparison Tx1 – Tx2		Treatment comparison Tx2 – Tx3		Arms	Baseline variance
				log HR	SE	log HR	SE		
CLL14	GClb	VenG		0.023	0.272			2	
CLL10	FCR	BR		0.033	0.261			2	
MaBLe	RClb	BR		−0.025	0.336			2	
iLLUMINATE	GClb	GIbr		−0.082	0.334			2	
Resonate-2	Clb	IBR		−0.799	0.268			2	
ECOG	FCR	IBR+R		−1.784	0.589			2	
COMPLEMENT1	Clb	OClb		−0.094	0.239			2	
Alliance	BR	IBR	IBR+R	0.109	0.306	0.069	0.309	3	0.065
CLL11	Clb	GClb	RClb	−0.755	0.246	−0.511	0.233	3	0.037

Abbreviations: BR: bendamustine plus rituximab; FCR: fludarabine, cyclophosphamide and rituximab; GClb: chlorambucil plus obinutuzumab; HR: hazard ratio; IBR+R: ibrutinib plus rituximab; RClb: chlorambucil plus rituximab; SE: standard error; Tx: treatment.

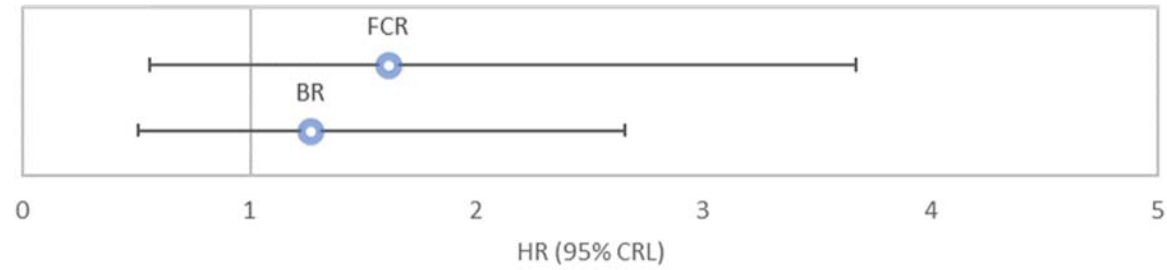
Table 10 shows the meta-analysis results on the hazard ratio of OS in the overall network. In Figure 3, the hazard ratio and the 95% credible intervals are presented visually. VenG shows comparable efficacy to all comparators, with overlapping credibility intervals. Results of the pairwise comparison of treatments can be found in Table 11.

Table 10: NMA results for OS in the network

Treatment	HR	CrI 2.5%	CrI 97.5%
VenG (reference)			
FCR	1.608	0.559	3.668
BR	1.263	0.508	2.648

*Numerical finding.
Abbreviations: BR: bendamustine with rituximab; CrI: credible interval; FCR: fludarabine, cyclophosphamide and rituximab; HR: hazard ratio; NMA: network meta-analysis; PFS: progression-free survival; VenG: venetoclax with obinutuzumab.

Figure 3: Hazard ratios and 95% credibility intervals for the NMA of OS



HRs above 1 should be interpreted as VenG having better efficacy than the comparator, HRs below 1 should be interpreted as giving preference to the comparator.
Abbreviations: BR: bendamustine plus rituximab; FCR: fludarabine, cyclophosphamide and rituximab; NMA: network meta-analysis; O+Clb: chlorambucil plus ofatumumab; OS: overall survival.

Table 11: Pairwise hazard ratios with 95% credibility intervals for the NMA of OS in the overall network (CLL14 update and Resonate-2 update)

	VenG	FCR	BR
VenG	1	1.7725 (0.8885, 3.1710)	1.4037 (0.8105, 2.2620)
FCR		1	0.8305 (0.5010, 1.2960)
BR			1

Abbreviations: BR: bendamustine plus rituximab; FCR: fludarabine, cyclophosphamide and rituximab; NMA: network meta-analysis; PFS: progression-free survival; VenG: venetoclax plus obinutuzumab.

A.1.5.3 Consistency check

The results from the NMA (indirect HRs in the loops of the networks) were compared to the direct HRs (retrieved directly from the trial publications) for both PFS and OS. The results of this comparison are given in Table 12. This comparison was performed to check the validity of the NMA results.

Table 12. Consistency check

Trial	Outcome	Intervention	Comparator	Direct HR	Inverse direct HR	Indirect HR	Difference
CLL10	PFS	BR	FCR	1.626	0.615	[redacted]	[redacted]
	OS	BR	FCR	1.034	0.967	[redacted]	[redacted]
MaBLe	PFS	BR	RClb	0.523	1.912	[redacted]	[redacted]
	OS	BR	RClb	0.975	1.026	[redacted]	[redacted]
ECOG	PFS	RIbr	FCR	0.352	2.841	[redacted]	[redacted]
	OS	RIbr	FCR	0.168	5.952	[redacted]	[redacted]
Alliance	PFS	Ibr	BR	0.370	2.703	[redacted]	[redacted]
	PFS	RIbr	BR	0.400	2.500	[redacted]	[redacted]
	OS	Ibr	BR	1.115	0.897	[redacted]	[redacted]
	OS	RIbr	BR	1.072	0.933	[redacted]	[redacted]

*The inverse of the direct HR was used to calculate the difference, since the inverse indirect HR was presented in the pairwise table only.
Abbreviations: BR: bendamustine with rituximab; FCR: fludarabine with cyclophosphamide and rituximab; HR: hazard ratio; Ibr: ibrutinib; OS: overall survival; PFS: progression-free survival; RClb: rituximab with chlorambucil; RIbr: rituximab with ibrutinib.

Overall, there was good consistency between the direct evidence and the generated indirect evidence. The only major inconsistencies identified relate the ECOG and the CLL10 trials. The ECOG and the CLL10 trials showed more heterogeneity compared to the other trials, mainly because of inclusion of fit patients instead of unfit patients. This is expected to have an impact on the pairwise hazard ratios.

A.1.5.4 WinBUGS code

The code for the NMA was based on the program 7b for fixed effects from : NICE TSD2 (Reference: http://nicedsu.org.uk/wp-content/uploads/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf)

- Rationale for using code: The network parameters in Example 7 were similar to our network in terms of the network structure, the aggregate data reflecting a comparison between the intervention and comparator in the trial and the presence of both 2 and three arm studies.
- Differences between the codes: The codes are identical except for the use of the 'inprod2' vs. 'inprod' command – this refers only to the run-speed for the model.
- Differences between the two networks (unfit / overall) : The same model specification was used for both the unfit (i.e., network without FCR) and overall networks (i.e., network with FCR+BR), the only thing that changed was the input file with different number of trials and comparators in the two networks for the outcomes.

Please see the uncommented WinBUGS code below:

```
# Normal likelihood, identity link, trial-level data given as treatment differences
# Fixed effects model
model{
for(i in 1:ns2) {
        y[i,2] ~ dnorm(delta[i,2],prec[i,2])
        resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
        }
for(i in (ns2+1):(ns2+ns3)) {
        for (k in 1:(na[i]-1)) {
                for (j in 1:(na[i]-1)) { Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k) }
        }
        Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])

        y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])

        for (k in 1:(na[i]-1)){
                ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
                z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
        }
        resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
        }
for(i in 1:(ns2+ns3)){
```



```
        for (k in 2:na[i]) {
                var[i,k] <- pow(se[i,k],2)
                prec[i,k] <- 1/var[i,k]
                delta[i,k] <- d[t[i,k]] - d[t[i,1]]
                }
        }
totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
}
```


A.1.6 *Discussion and conclusion*

In this analysis (including both unfit and fit patients), FCR and BR both performed numerically worse than VenG for PFS, but no difference was found in OS (credible intervals cross 1). This trend aligns with general trend seen in CLL14 results.

Some limitations of the network meta-analysis should be taken into account. The proportional hazards assumption was not tested in the included trial publications and might have been violated. Furthermore, given that only one study per comparison arm was available, only fixed effect models were used in the analysis. Including more direct evidence in the network, had it been available, might have contributed to more robust estimates.

A.2 Cost effectiveness vs FCR/BR

All data provided in this economic analysis are based on the company's NICE addendum model as opposed to the ERG model. For external comparators (Ibrutinib, FCR, BR), in the absence of robust evidence base, a conservative approach was taken to model subsequent treatments.

A.2.1 *Clinical parameters and variables*

A.2.1.1 Adverse event probabilities

Table 13 provides an overview of the adverse event (AE) probabilities utilised in the cost-effectiveness model.

Table 13: Probabilities for serious treatment-emergent AEs utilised in the cost-effectiveness model (Grade 3–5)

AE Incidence	FCR	BR
Asthenia	0.00%	0.00%
Diarrhoea	0.00%	7.00%
Dyspnoea	0.00%	0.00%
Febrile neutropenia	0.00%	0.00%
Infusion related reaction	0.00%	0.00%
Leukopenia	24.00%	48.00%
Neutropenia	34.00%	59.00%
Pneumonia	0.00%	9.00%
Sepsis	0.00%	1.00%
Thrombocytopenia	7.00%	14.00%
Source	Hallek 2010[21]	Eichhorst 2016[11]
Sample size	404	279

Abbreviations: AE: adverse event; BR: bendamustine with rituximab; FCR: fludarabine, cyclophosphamide and rituximab.

A.2.2 *Cost and healthcare resource use identification*

The same healthcare costs and resource use, as presented in the addendum, were utilised in this analysis where appropriate. Intervention and comparator costs and resource use specific to this analysis are detailed within this section.

A.2.2.1 Intervention and comparator costs and resource use

The British National Formulary (BNF) online database was used to source the drug costs for all the treatment regimes. Table 14 is an overview of all the drugs included in this analysis along with the cost per pack size and the cost per mg of the drug. Table 15 is an overview of the subsequent treatment mix.

Table 14: Drug costs for comparators

Drug	Dose per tablet or vial	Units per package	Cost per package	Price per mg	Source
Fludarabine					
Tablet	10 mg	15	£302.48	£2.02	BNF
Tablet	10 mg	20	£403.31	£2.02	BNF
Cyclophosphamide					
Tablet	50 mg	100	£139.00	£0.03	BNF
Bendamustine					
IV	25 mg	1	£2.91	£0.12	eMIT national database (NPC code: DZR040)[22]

Abbreviations: BNF: British national formulary; IV: Intravenous.

Table 15: Overview of subsequent treatment mix

Treatment at entry	Ibrutinib	VenR	Ven monotherapy
FCR	50.0%	50.0%	0.0%
BR	50.0%	50.0%	0.0%

Abbreviations: BR: bendamustine with rituximab; FCR: fludarabine, cyclophosphamide and rituximab; Ven: venetoclax; VenR: venetoclax with rituximab.

A.2.3 *Base case incremental cost-effectiveness analysis results*

The base case deterministic cost-effectiveness results are provided for list price and with venetoclax PAS price in Table 16 and Table 17, respectively. In the All 1st line CLL population, VenG was associated with higher average quality-adjusted life years (QALYs) and higher average costs versus FCR and BR. The driver of those results is the VenG medication cost, which reduced substantially when the commercial discount was incorporated in the model. It is anticipated that results will improve once comparator commercial discounts are also incorporated.

Table 16: Base case results at VenG list price (deterministic)

Treatment	Total costs, £	Total LYG	Total QALYs	Incremental costs, £ (versus VenG)	Incremental LYG (versus VenG)	Incremental QALYs (versus VenG)	ICER, £/QALY (versus VenG)
All 1st line CLL population							
FCR	[redacted]	10.849	5.585	[redacted]	3.063	2.066	[redacted]
BR	[redacted]	12.384	5.931	[redacted]	1.529	1.720	[redacted]
VenG	[redacted]	13.912	7.651				

Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Table 17: Base case results at VenG PAS price* (deterministic)

Treatment	Total costs, £	Total LYG	Total QALYs	Incremental costs, £ (Versus VenG)	Incremental LYG (Versus VenG)	Incremental QALYs (Versus VenG)	ICER, £/QALY (Versus VenG)
All 1st line CLL population							
FCR	[redacted]	10.849	5.585	£60,164	3.063	2.066	£29,125
BR	[redacted]	12.384	5.931	£53,429	1.529	1.720	£31,065
VenG	[redacted]	13.912	7.651	-	-	-	-

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators.
Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

A.2.4 *Probabilistic sensitivity analysis (PSA)*

PSA were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 simulations, in order to calculate the uncertainty in costs and outcomes. In cases where uncertainty data were not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The base case probabilistic results for list price and with venetoclax PAS price are provided in Table 18 and Table 19, respectively. The probabilistic results are broadly in line with the deterministic results, showing that the model is relatively stable when tested for uncertainty and that VenG is more expensive and more efficacious, but it is not cost-effective at the threshold of £30,000/QALY versus FCR and BR. It is anticipated that results will improve once comparator commercial discounts are also incorporated.

Table 18: Base case results at VenG list price (probabilistic)

Treatment	Total costs, £ (95% CI)	Total LYG	Total QALYs (95% CI)	Incremental costs, £ (versus VenG)	Incremental LYG	Incremental QALYs (versus VenG)	ICER, £/QALY (versus VenG)
All 1st line CLL population							
FCR	[redacted]	NR	5.733 (3.579,7.608)	[redacted]	NR	1.860	[redacted]
BR	[redacted]	NR	5.930 (4.145, 7.468)	[redacted]	NR	1.663	[redacted]
VenG	[redacted]	NR	7.592 (6.265, 8.739)				

Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Table 19: Base case results at VenG PAS price* (probabilistic)

Treatment	Total costs, £ (95% CI)	Total LYG	Total QALYs (95% CI)	Incremental costs, £ (versus VenG)	Incremental LYG	Incremental QALYs (versus VenG)	ICER, £/QALY (versus VenG)
All 1st line CLL population							
FCR	[redacted]	NR	5.718 (3.616,7.527)	£67,246	NR	1.856	£36,236
BR	[redacted]	NR	5.918 (4.024,7.366)	£61,091	NR	1.656	£36,901
VenG	[redacted]	NR	7.574 (6.214,8.720)		-		

*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators.
Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

The model results from the PSA are presented in the scatter plot at list price in Figure 4 and at venetoclax PAS price in Figure 5. Similar to the deterministic results, VenG is more expensive and more efficacious versus FCR and BR in the PSA also.

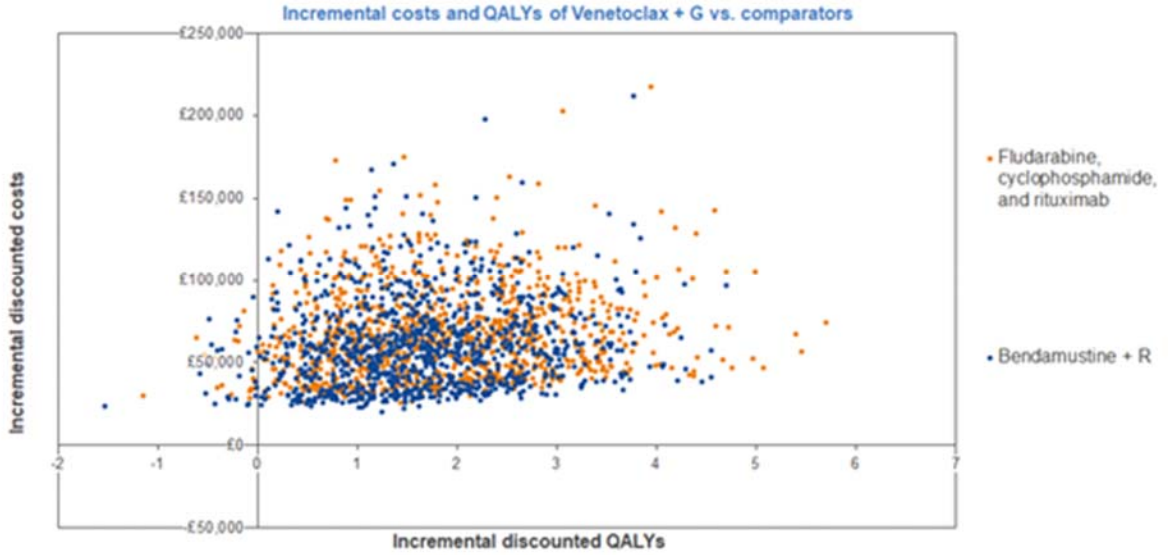
The total cost and QALY estimates are comparable between the deterministic and the probabilistic analyses (differ between [redacted] for incremental total costs at list price and [redacted] at venetoclax PAS price; and [redacted] for QALYs at list price and [redacted] at venetoclax PAS price, due to stochastic variation between model runs).

Figure 6 and Figure 7 display the cost-effectiveness acceptability curve at different values of WTP at list price and venetoclax PAS price, respectively. At a £30,000/QALY threshold, at list price and venetoclax PAS price, VenG has over [redacted] and 31% probability, respectively, of being cost-effective compared to FCR and BR.

Figure 4: Scatter plot of probabilistic results on the cost-effectiveness plane for All 1st line CLL population (list price)

Abbreviations: Bendamustine + R: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 5: Scatter plot of probabilistic results on the cost-effectiveness plane for All 1st line CLL population (venetoclax PAS price)*

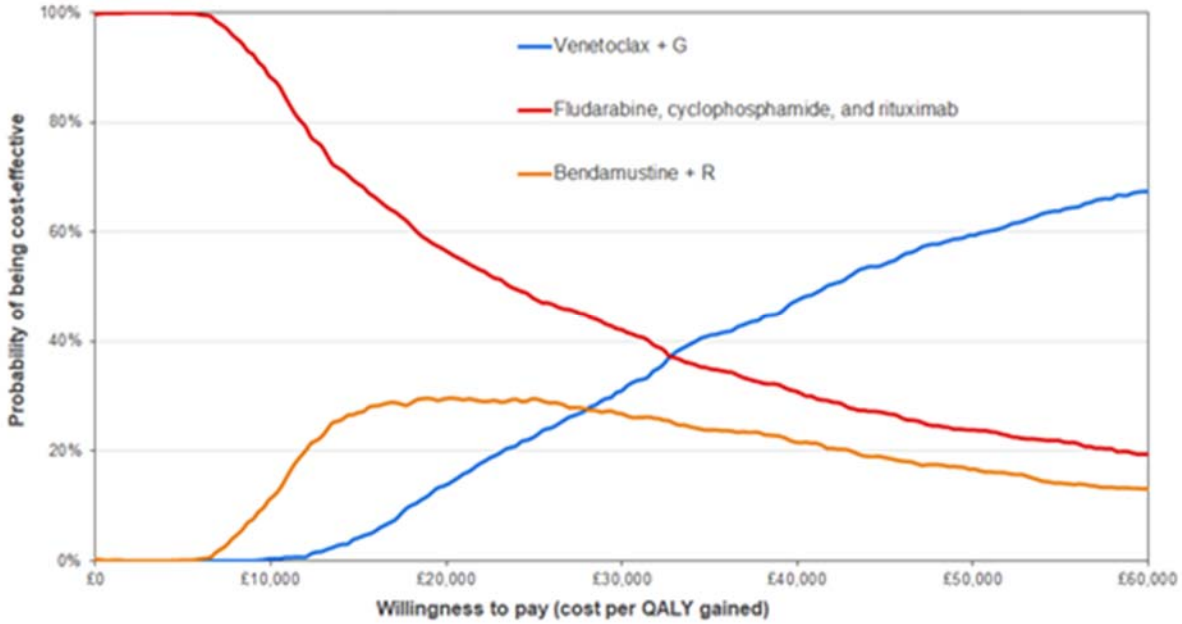


*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators.
Abbreviations: Bendamustine + R: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 6: Cost-effectiveness acceptability curves for All 1st line CLL population (list price)

Abbreviations: Bendamustine + R: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

Figure 7: Cost-effectiveness acceptability curves for All 1st line CLL population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators.
Abbreviations: Bendamustine + R: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; QALY: quality-adjusted life year; Venetoclax + G: venetoclax with obinutuzumab.

A.2.5 *Deterministic sensitivity analysis*

All 1st line CLL population (VenG versus FCR)

Figure 8, Figure 9 and Figure 10 present the tornado plots from the one-way deterministic sensitivity analysis for incremental costs, QALYs and ICER, respectively, for VenG versus FCR at list price. Figure 11, Figure 12 and Figure 13 present the same data at venetoclax PAS price.

In cases where uncertainty data was not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The greatest impact on incremental costs is due to the OS hazard ratio of FCR versus VenG. The OS curve drives the FCR survival curves and the survival curves are the key determinant of the incremental costs in the model. The greatest driver of incremental QALYs and of the incremental cost per QALY is also the OS HR.

Figure 8: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus FCR) for All 1st line CLL population (list price)

Abbreviations: AE: adverse event; CLL: chronic lymphocytic leukaemia; CT: computed tomography; FCR: fludarabine, cyclophosphamide and rituximab; HR: hazard ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: overall survival, VenG: venetoclax with obinutuzumab.

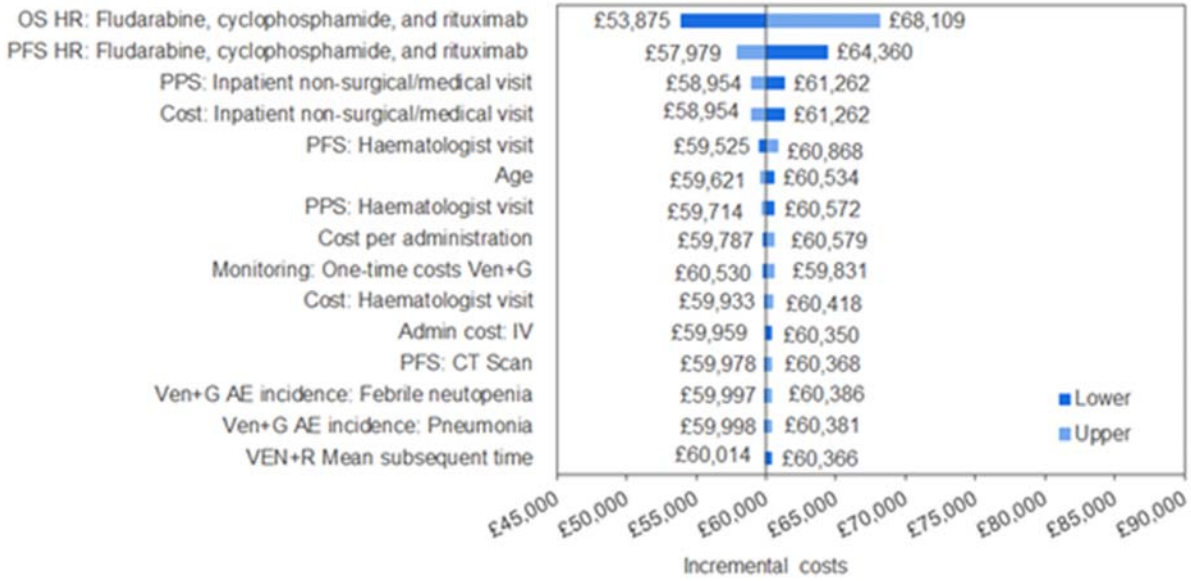
Figure 9: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus FCR) for All 1st line CLL population (list price)

Abbreviations: AE: adverse event; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; FTD: fixed treatment duration; HR: hazard ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: overall survival, QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Figure 10: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus FCR) for All 1st line CLL population (list price)

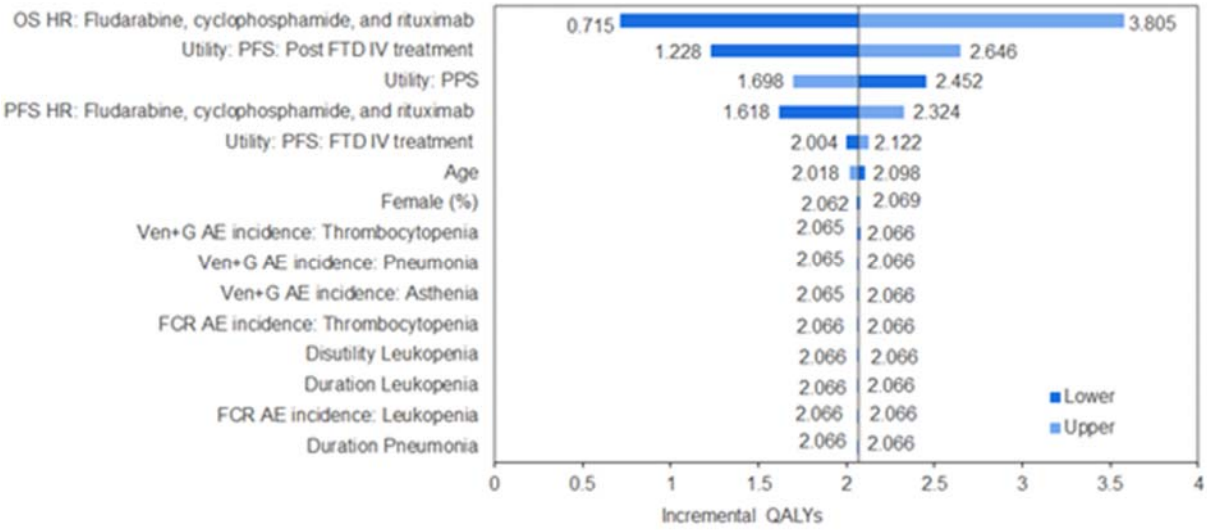
Abbreviations: AE: adverse event; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; FTD: fixed treatment duration; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: overall survival, VenG: venetoclax with obinutuzumab.

Figure 11: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus FCR) for All 1st line CLL population (venetoclax PAS price)*



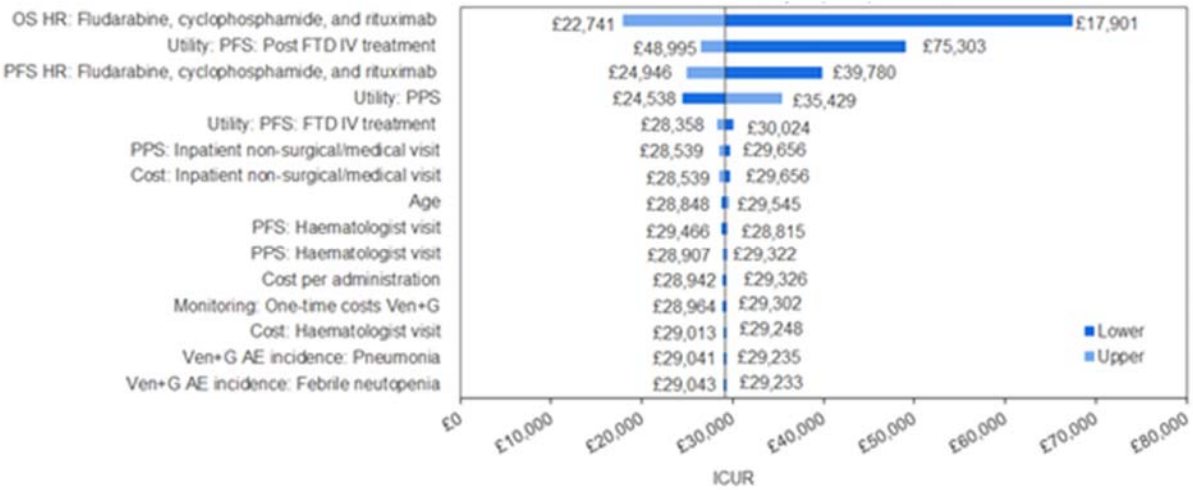
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators.
Abbreviations: AE: adverse event; CLL: chronic lymphocytic leukaemia; CT: computed tomography; FCR: fludarabine, cyclophosphamide and rituximab; HR: hazard ratio; IV: intravenous; PAS: Patient Access Scheme; PFS: progression-free survival; PPS: post-progression survival; OS: overall survival, VenG: venetoclax with obinutuzumab.

Figure 12: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus FCR) for All 1st line CLL population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators. **Abbreviations:** AE: adverse event; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; FTD: fixed treatment duration; HR: hazard ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: overall survival, QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Figure 13: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus FCR) for All 1st line CLL population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of comparators. **Abbreviations:** AE: adverse event; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; FTD: fixed treatment duration; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; IV: intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: overall survival, VenG: venetoclax with obinutuzumab.

All 1st line CLL population (VenG versus BR)

Figure 14, Figure 15 and Figure 16 present the tornado plots from the one-way deterministic sensitivity analysis for incremental costs, QALYs and ICER, respectively, for VenG versus BR at list price. Figure 17,Figure 18, and Figure 19 present the same data at venetoclax PAS price.

In cases where uncertainty data was not available for an input, variability (i.e. standard error) of 10% of the mean values was assumed.

The greatest impact on incremental costs is due the OS hazard ratio of BR versus VenG. The OS hazard ratio drives the BR survival curves and the survival curves are the key determinant of the incremental costs in the model. The greatest driver of incremental QALYs is also the OS hazard ratio. However, the key driver of the incremental cost per QALY is the PFS utility following the FTD period value. Since a large proportion of patients in the VenG arm remain in the PFS following the FTD period compared to BR, the QALYs accrued in this health state have the largest impact on the cost per QALY.

Figure 14: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus BR) for All 1st line CLL population (list price)

Abbreviations: AE: Adverse event; BR/ bendamustine + R: bendamustine with rituximab; CT: computed tomography; FTD: Fixed treatment duration; HR: Hazard ratio; IV: Intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: Overall survival, VenG: venetoclax with obinutuzumab.

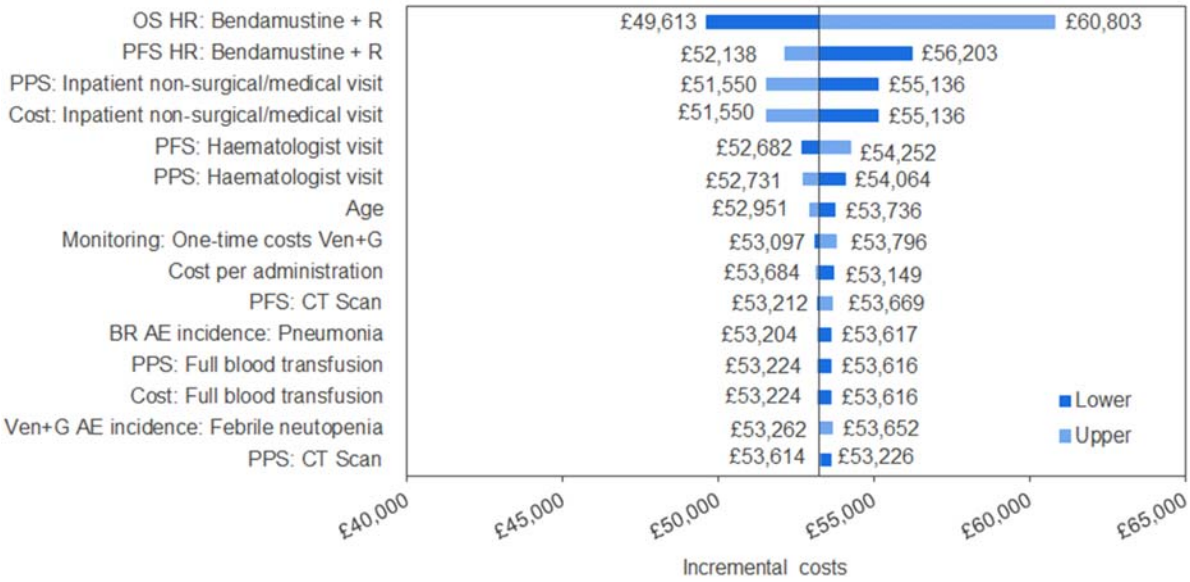
Figure 15: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus BR) for All 1st line CLL population (list price)

Abbreviations: AE: Adverse event; BR/ bendamustine + R: bendamustine with rituximab; FTD: Fixed treatment duration; HR: Hazard ratio; IV: Intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: Overall survival, VenG: venetoclax with obinutuzumab.

Figure 16: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus BR) for All 1st line CLL population (list price)

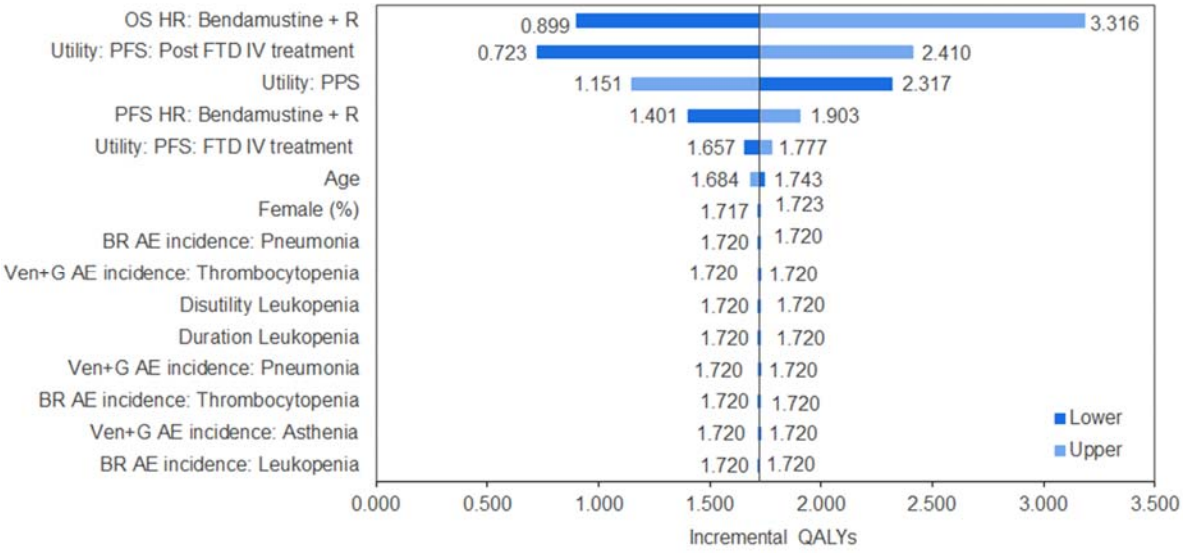
Abbreviations: AE: Adverse event; BR/ bendamustine + R: bendamustine with rituximab; CT: computed tomography; FTD: Fixed treatment duration; HR: Hazard ratio; IV: Intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: Overall survival, VenG: venetoclax with obinutuzumab.

Figure 17: Tornado plot of deterministic sensitivity analysis: impact on incremental costs (VenG versus BR) for All 1st line CLL population (venetoclax PAS price)*



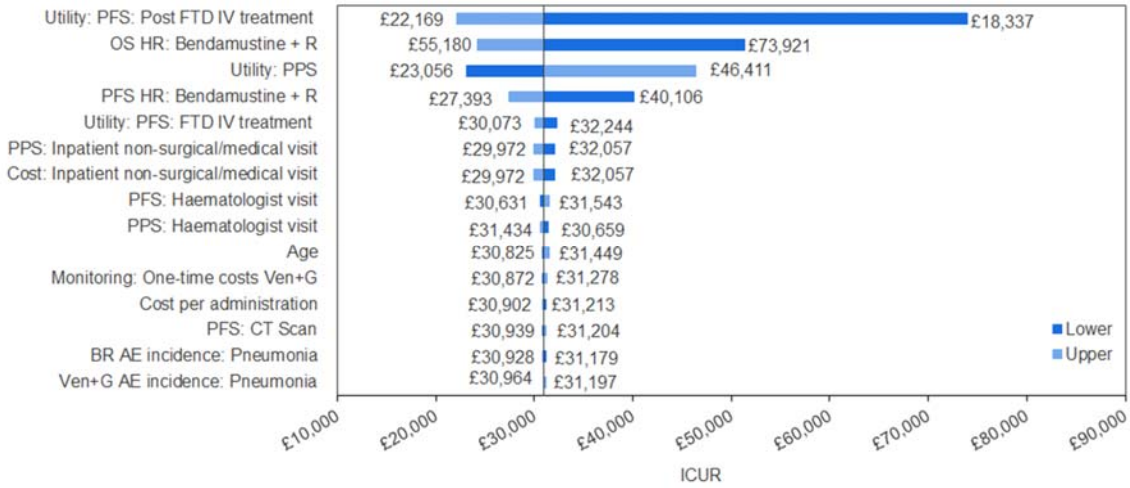
*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: AE: Adverse event; BR/ bendamustine + R: bendamustine with rituximab; CT: computed tomography; FTD: Fixed treatment duration; HR: Hazard ratio; IV: Intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: Overall survival, VenG: venetoclax with obinutuzumab.

Figure 18: Tornado plot of deterministic sensitivity analysis: impact on incremental QALYs (VenG versus BR) for All 1st line CLL population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: AE: Adverse event; BR/ bendamustine + R: bendamustine with rituximab; FTD: Fixed treatment duration; HR: Hazard ratio; IV: Intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: Overall survival, VenG: venetoclax with obinutuzumab.

Figure 19: Tornado plot of deterministic sensitivity analysis: impact on ICER (VenG versus BR) for All 1st line CLL population (venetoclax PAS price)*



*This analysis only includes the PAS price of venetoclax and does not include the PAS price of obinutuzumab.
Abbreviations: AE: Adverse event; BR/ bendamustine + R: bendamustine with rituximab; FTD: Fixed treatment duration; HR: Hazard ratio; IV: Intravenous; PFS: progression-free survival; PPS: post-progression survival; OS: Overall survival, VenG: venetoclax with obinutuzumab.

A.2.5.1 Summary of sensitivity analyses results

The base case average probabilistic ICER is closely aligned with the base case deterministic ICER for both comparators. At the £30,000/QALY threshold typically applied in NICE appraisals, at venetoclax net price, VenG, FCR, and BR were found to have a 31%, 42%, and 27% probability of being the cost-effective option in the base case, in the All 1st line CLL populations.

A.3 Scenario analysis of subsequent treatment modelling

A.3.1 *Methodology*

When applying subsequent treatment costs three key inputs are required:

1. The type of treatment mix received
2. The timepoint at which the patients who are eligible to receive the next treatment line will receive therapy
3. How long subsequent (second line onwards) treatment is received, i.e. how long patients stay on second and later lines of treatment

The steps taken to inform these key inputs are provided below:

1. The subsequent treatment mix assumptions have not been changed between the previous Addendum model and the updated version.
2. The TTNT curves for the VenG and GClb arms from the CLL14 trial were used to identify the number of patients in each cycle who move to the next line (i.e. second line) of treatment. For ibrutinib, the approach remains the same as the previous Addendum model.
3. The shortest subsequent treatment duration is chosen between the modelled and literature values. In other words, the subsequent treatment duration is constrained by the duration reported in literature.

To calculate the modelled subsequent treatment duration, for VenG and GClb, the difference between the OS and time-to-next treatment (TTNT) curves was taken. For ibrutinib, this time period was calculated by taking the difference between the OS and PFS curves.

To constrain the subsequent treatment duration by the literature values, the lowest treatment duration between 'modelled subsequent treatment duration' and 'mean time on treatment' reported in literature was selected. **Therefore, ensuring that the duration on subsequent treatment does not exceed the literature values and the literature values act as a ceiling for time on subsequent treatment.**

In the model, for the VenG and ibrutinib arms, the **modelled** time on subsequent treatment is used and, for the GClb arm, the **literature** time on subsequent treatment is used.

In summary, a total cost of subsequent treatment which is constrained by the duration on subsequent treatment is being multiplied by the incident patients who are eligible to receive the next line of treatment per cycle.

A.3.2 *Overview of changes in model cells*

1. 'Costs' sheet: Cells J87: Q98
2. 'Input conversion': Cells C49:D51

3. ‘Costs total’: Cells N29:P420; AF29:AH420

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Technical engagement response form

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Thursday 2 July 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Leukaemia Care**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Questions for engagement

Issue 1: Patient population	
Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal?	**There are significant unmet needs in both populations and therefore the treatment should be considered as separately relevant for both.** **The population unfit for FCR or BR are in need of a greater choice in the number of treatments available to them, as being unsuitable for FCR or BR immediately reduces the options. They are also in need of an option that is of fixed duration, which our research shows many favour over continuous therapies such as ibrutinib.** **However, the population suitable for FCR or BR are also in need of alternative treatments. Whilst the lack of the 17p deletion or TP53 mutation means that FCR and BR can still be effective, greater choice is important for patients. Additionally, the side effects of these chemo-immunotherapeutic agents, particularly long term immune system effects, are being seen as increasingly unfavourable by patients and clinicians, compared with newer treatments such as this.** **We appreciate that the challenges in the data available for this indication but ask that NICE requests this information from the company and considers it. We also ask that the committee considers use of the CDF to help resolve uncertainties in this group.** **Additionally, all patients can access a similar treatment, venetoclax with rituximab, upon relapse. It is unethical for some patients to wait until relapse before accessing treatments that can offer significant benefits to them, whilst allowing access to another population earlier in the pathway.** As mentioned in previous documents, restricting access to those who are unsuitable to FCR also creates inequity of access to treatment by age, as most of those who are unfit for chemotherapy are

	frail due to their age. This leaves the younger people with fewer choices of treatments and they must risk the long term side effects of the chemoimmunotherapy before they can try newer treatment options.
Is the patient population in the CLL14 trial appropriate for decision-making, particularly in the company's subgroup without a del(17p)/TP53 mutation?	**Yes, this is the most recent data available.**
Issue 2: The most plausible PFS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which PFS extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	**No comment.**
Issue 3: The most plausible OS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which overall survival (OS) extrapolation model is most plausible for GClb in the patient population without del(17p)/*TP53* mutation?	**No comment**
Issue 4: Subsequent treatment costs	

Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?	No comment
Which TTNT extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	No comment
Issue 5: Indirect comparison hazard ratios: Del(17p)/*TP53*-mutated population	
Which PFS and OS hazard ratios are most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation?	No comment
Issue 6: OS and PFS extrapolations: Del(17p)/*TP53*-mutated population	
Do you agree with the company's approach to modelling the OS and PFS curves for VenG and ibrutinib in patients with del(17p)/*TP53* mutation?	No comment
Issue 7: Pre-progression off-treatment utility	

Which is the more plausible utility value for the 'pre-progression off treatment' health state: the company's base-case value of 0.82 derived from the company's submission for TA343, or the ERG's re-calculated value of 0.77 based on the gender-weighted, age-specific value of the general population?	No comment
Issue 8: Quality of life impact of venetoclax with obinutuzumab	
Does the PFS benefit of VenG over GClb in previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation translate into improved patient quality of life?	Yes. As stated in our submission, patients prefer non-chemotherapeutic treatments due to the reduced adverse events, especially long term adverse event.

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Technical engagement response form

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[redacted]

Questions for engagement

Issue 1: Patient population	
Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal?	Yes absolutely. The German GAIA/CLL13 study directly compares FCR against VenG and is currently in follow-up. Awaiting these data, we have to compare data from the most recent UK study of fit patients with CLL treated upfront with FCR (Admire). This showed: UK Admire bone marrow MRD 50.5%, PFS at 2 years: 80%; SAEs requiring hospitalisation: 43.4% This compares against VenG: Bone marrow MRD 56.9%; 88.2% PFS at 2 years Minimal Residual Disease (MRD) is an FDA and EMA accepted surrogate marker for PFS and extremely useful as therapies are becoming more and more effective and PFS longer. From above we can therefore conclude that VenG is at least non-inferior and probably superior to FCR with respect to efficacy. Moreover, we have to bear in mind that the VenG treated cohort in CLL14 was a cohort of older patients with co-morbidities. As clinicians we know that these two factors are inversely correlated with good outcome and we therefore know intuitively that VenG is definitely superior to FCR with respect to efficacy in fit patients. VenG is also clearly superior to FCR with respect to safety, and hospital admissions for SAEs are rare. BR is not NICE approved for patients with CLL, and inferior to FCR with respect to efficacy, esp in young patients (German CLL10).

Is the patient population in the CLL14 trial appropriate for decision-making, particularly in the company's subgroup without a del(17p)/TP53 mutation?	Yes, the patient population is representative of about two-third of patients with CLL who are either elderly and/or with significant co-morbidities requiring first treatment.
Issue 2: The most plausible PFS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which PFS extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	The results for 2-year PFS in GClb arms of CLL11 and CLL14 is comparable at about 60%. Treatment dose regimen for GClb in the two studies was the same and the patient cohort is also comparable. The ERG's approach to use the 5-year observed PFS for GClb as a calibrator to model the 5 and 10-year PFS of VenG is therefore plausible.
Issue 3: The most plausible OS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which overall survival (OS) extrapolation model is most plausible for GClb in the patient population without del(17p)/*TP53* mutation?	I do not agree with the approach taken by ERG as it is based on OS of historical trials that reported OS at a time when access to the novel therapies was not available. CLL11 reported in 2014 well before Ibrutinib was made widely available for treatment of relapses of patients recruited into CLL11. RESONATE reported before Venetoclax became available as a subsequent line of therapy for patients relapsing after ibrutinib. It is therefore worrying that the ERG's extrapolation of CLL14 match the 5-year OS of GClb treated patients in CLL11 as these patients' OS would be expected to be far inferior to that of patients treated with GClb in CLL14, simply because the latter will have options like Ibrutinib or Ven+R or Ven monotherapy at relapse available to them that were not available for patients relapsing after treatment on CLL11 protocol. For example, an analysis of real-world data from the US and the UK by Mato et al Clin Cancer Res 2020 (doi: 10.1158/1078-0432.CCR-19-3815) clear shows benefit of Ibrutinib after relapse

	from Venetoclax with/without anti-CD20 with a PFS at 24 months of 78%. While this is mainly in patients who received CIT in frontline, Venetoclax at 1st relapse and Ibrutinib at 2nd relapse, it is clinically plausible to assume that PFS 2 after ibrutinib will be even longer if the previous therapy was frontline VenO and not Ven in relapse.
Issue 4: Subsequent treatment costs	
Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?	TTNT: Following on from relapse from chemo-immunotherapy, patients often do not require immediate treatment. The median TTNT is 11 months after first relapse. This TTNT decreases with number of prior therapies and time from diagnosis. For example, it is not unusual to switch patients directly from 1st relapse Ibrutinib to 2nd relapse Venetoclax without any treatment free interval. Duration of relapse treatment: The relapse treatment is either with continuous Ibrutinib or fixed-duration Ven-R over 24 months or continuous Ven mono. Real-world UK data suggests that about one third of patients will discontinue Ibrutinib therapy within the first 2 years most commonly due to side-effects. Ibrutinib dose reductions are also common and described in the real-world data papers. All of these have to be taken into account when calculating subsequent treatment costs.

Which TTNT extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	As mentioned above, is not plausible to use CLL11 for anything other than the 5-year PFS curve modelling. This is because at the time of CLL11 none of the targeted therapies were available. For example, subsequent treatment of relapse after GClb on CLL11 would have been with dose-intense chemotherapy. In frail patients, this would have been delayed as long as possible to avoid treatment side-effects prolonging TTNT. In the era of targeted therapy, TTNT is often shorter as subsequent targeted therapies are so much better tolerated.
Issue 5: Indirect comparison hazard ratios: Del(17p)/*TP53*-mutated population	
Which PFS and OS hazard ratios are most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation?	The only frontline study of ibrutinib in patients with TP53 disrupted CLL is from Farooqui M et al Lancet Onc 2015 (n=32) with a PFS of 91% and OS of 84% at two years in this group. These data should be comparable with CLL14 as the two patient cohorts are similar and the Farooqui study is recent enough for patients who relapse to benefit from the arrival of Venetoclax as relapse therapy. With regards to PFS, VenG compares less favourably to Ibrutinib (PFS: 70%). However, it is important to note that VenG is given over 12 months only and not continuously as ibrutinib. This is likely to affect its efficacy in the with TP53 abnormalities. As clinicians, we would feel more comfortable giving Ven-G over two years in this high-risk group.

	Clearly, VenG is far better tolerated than Ibrutinib and should be made available to this high-risk group of patients for whom no other options apart from Ibrutinib are available.
Issue 6: OS and PFS extrapolations: Del(17p)/*TP53*-mutated population	
Do you agree with the company's approach to modelling the OS and PFS curves for VenG and ibrutinib in patients with del(17p)/*TP53* mutation?	The company's 5-year PFS of 37.99% following 12 months of VenO is realistic for this high-risk population. Added on top of this would be an expected PFS at 24 months of 78% with Ibrutinib (Mato et al Clin Cancer Res 2020 (doi: 10.1158/1078-0432.CCR-19-3815)). It means that the 5 year OS of 47.16% for VenG followed by Ibrutinib predicted by the company seems too pessimistic.
Issue 7: Pre-progression off-treatment utility	
Which is the more plausible utility value for the 'pre-progression off treatment' health state: the company's base-case value of 0.82 derived from the company's submission for TA343, or the ERG's re-calculated value of 0.77 based on the gender-weighted, age-specific value of the general population?	No comment; please refer to stats advice
Issue 8: Quality of life impact of venetoclax with obinutuzumab	

Does the PFS benefit of VenG over GClb in previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation translate into improved patient quality of life?	It certainly does. The problem here is that the validated patient questionnaires to collect PRO are completely useless (sorry) and not sensitive/granular enough to pick up any significant differences in QoL. This is a common problem for all CLL trials and as clinicians we are aware. VenG is extremely well tolerated. Patients achieve a fast and deep remission leading to complete resolution of systemic symptoms and a decrease in infection rates. The same is not true for GClb where responses are often delayed and immune/bone marrow suppression leads to infection. When looking after patients treated with either VenG or GClb, it is clear that those who achieve deep responses benefit most in respect to QoL thanks to less fatigue, fewer residual symptoms and better overall immune function.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm** on **Thursday 2 July 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
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About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Joint response for CLL Support and Lymphoma Action**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Patient population	
Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal?	**Yes**
Is the patient population in the CLL14 trial appropriate for decision-making, particularly in the company's subgroup without a del(17p)/TP53 mutation?	**No. We advocate for all patient populations to be considered for this treatment so to consider only specific subgroups is not appropriate.** The company submission limits the positioning of VenG to the treatment of previously untreated FCR or BR unsuitable patients without del(17p)/*TP53* mutation and the treatment of previously untreated patients with del(17p)/*TP53* mutation. This is narrower than the NICE scope and EMA marketing authorisation indication, which covers patients with previously untreated CLL regardless of mutation status or suitability to receive FCR or BR. We are disappointed that the company did not consider FCR or BR to be relevant comparators despite both being included in the NICE scope and therefore did not provide data for these comparisons.

Issue 2: The most plausible PFS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which PFS extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	**2 knot hazard spline model predicts observed data so this may be the most plausible**
Issue 3: The most plausible OS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which overall survival (OS) extrapolation model is most plausible for GClb in the patient population without del(17p)/*TP53* mutation?	**Unable to comment**
Issue 4: Subsequent treatment costs	
Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?	Unable to comment
Which TTNT extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	Unable to comment

Issue 5: Indirect comparison hazard ratios: Del(17p)/*TP53*-mutated population	
Which PFS and OS hazard ratios are most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation?	Unable to comment
Issue 6: OS and PFS extrapolations: Del(17p)/*TP53*-mutated population	
Do you agree with the company's approach to modelling the OS and PFS curves for VenG and ibrutinib in patients with del(17p)/*TP53* mutation?	Unable to comment
Issue 7: Pre-progression off-treatment utility	
Which is the more plausible utility value for the 'pre-progression off treatment' health state: the company's base-case value of 0.82 derived from the company's submission for TA343, or the ERG's re-calculated value of 0.77 based on the gender-weighted, age-specific value of the general population?	Unable to comment
Issue 8: Quality of life impact of venetoclax with obinutuzumab	

Does the PFS benefit of VenG over GClb in previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation translate into improved patient quality of life?	Yes. Please refer to our previously submitted gathered evidence from patient surveys indicating a greatly improved QOL.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**UK CLL Forum**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**For the UK CLL Forum:** Roche (£20,000) –for last 2 years Janssen (£7,000) –per year, in 2 payments, one for each meeting Abbie (£10,000) – per year £5,000 for the Autumn 2019 meeting and £5,000 for the Spring 2020 meeting AZ (£10,000) – per year [redacted]: Abbvie consultancy, meeting attendance, speaker, ad board Gilead meeting attendance, ad board Janssen meeting attendance, ad board, speaker

	[redacted]: honoraria from AbbVie, Roche, Gilead, Janssen and Astra Zaneca [redacted]: speaker fees and honoraria from Janssen and Gilead [redacted]: Roche for speaker fee AbbVie for advisory board, speaker fee, and travel/ conference attendance at ASH Astra Zeneca for advisory board Takeda for speaker fee [redacted]: AbbVie: Travel/conference support, remunerated speaker and consultant, Astra Zeneca: Remunerated speaker and consultant, Gilead: Research funding, travel/conference support, remunerated speaker and consultant, Janssen: Travel/conference support, remunerated speaker and consultant, Roche: Research funding, travel/conference support, remunerated speaker and consultant [redacted]: conferences and meetings attendance by AbbVie, Janssen and Gilead, ad board for Astra Zeneca

Questions for engagement

Issue 1: Patient population	
Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal?	**Yes for the following reasons –** **1. The CIRS score is not widely used in the UK, and as such the CLL14 population does not map cleanly on to UK practice. We think it is highly likely that many patients entered into CLL14 would have been regarded as suitable for FCR/BR therapy in the UK, especially as more than 60% of the CLL14 patient population were under the age of 75 years.** **2. Improved PFS was especially favoured in the Venetoclax-Obinutuzumab arm in this younger age group (HR 0.28 (0.16-0.48) for <75 years; HR 0.48 (0.25-0.93) for >75 years). Currently patients in the UK can be entered into the FLAIR clinical study (comparing FCR to ibrutinib containing regimens) up to the age of 75 and it is likely many of these patients may have had a CIRS score of greater than 6. FLAIR also includes patients with a creatinine clearance <70 but above 50.** **3. FCR/BR chemoimmunotherapy regimes leave a significant area of unmet clinical need for 'fit' patients considered suitable for these therapies who do not have a del(17p)/*TP53* mutation, but who have unmutated *IGVH*. These patients have significantly worse PFS with chemoimmunotherapy compared to patients with mutated *IGVH*, (3 year PFS 63% versus 88%) (Shanafelt et al, 2019, DOI: 10.1056/NEJMoa1817073). There was no difference seen between mutated and unmutated *IGVH* populations treated with venetoclax-obinutuzumab in the CLL14 trial (90.3% versus 89.4% 2 year PFS).**

Is the patient population in the CLL14 trial appropriate for decision-making, particularly in the company's subgroup without a del(17p)/TP53 mutation?	**Yes – apart from caveat that we think several participants would have received FCR/BR in the UK.**
Issue 2: The most plausible PFS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which PFS extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	**None of the models are really ideal but finding a PFS which fits best with the CLL 11 and ERIC data seems most pragmatic. Therefore the 2-knot hazard spline model looks the best of the not so great options. A model aligning with the known CLL11 and ERIC PFS of 42 months would possibly have been better, especially when considering PFS.**
Issue 3: The most plausible OS extrapolation: Non-del(17p)/*TP53*-mutated population	
Which overall survival (OS) extrapolation model is most plausible for GClb in the patient population without del(17p)/*TP53* mutation?	**The choice of salvage therapy has significantly changed since 2014 when access to ibrutinib was not available: this makes using the CLL 11 study for OS modelling inappropriate. Therefore, we believe using the ERIC data is a better option – albeit with its limitations of being retrospective and perhaps patients' adherence to therapy may not be the same as that achieved in a clinical trial. It at least reflects more ready access to the new therapies which will obviously alter OS. Clearly having CLL which requires treatment must carry an increased risk of shortened survival and hence the company modelling lacks credibility. Overall we think the company estimations of 20 year survival is better than we would expect for the GClb treated group. The ERG OS modelling using the OS ERIC hazard rate from 3 years reduces the 20 year survival to something we think is more realistic for this patient group.**
Issue 4: Subsequent treatment costs	

Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?	**Yes due to the continuous nature of salvage treatments.**
Which TTNT extrapolation model is most plausible for VenG and GClb in the patient population without del(17p)/*TP53* mutation?	**Given the link between PFS and TTNT similar methods should be used for the two analyses and hence a method similar to the 2-knot hazard spline model used for PFS would seem sensible. We note that the ERGs chosen methods give almost identical figures for PFS and TTNT at 20 years which is what one would expect.**
Issue 5: Indirect comparison hazard ratios: Del(17p)/*TP53*-mutated population	
Which PFS and OS hazard ratios are most appropriate for the comparison of VenG with ibrutinib in patients with del(17p)/*TP53* mutation?	**We note the very small number of patients. Clearly if the aim is to compare ibrutinib with VenG then one can't use any data derived from GClb treated patients in CLL14. So we would suggest using [redacted] HR for PFS and [redacted] for OS.**
Issue 6: OS and PFS extrapolations: Del(17p)/*TP53*-mutated population	
Do you agree with the company's approach to modelling the OS and PFS curves for VenG and ibrutinib in patients with del(17p)/*TP53* mutation?	**No as includes data from GClb treated patients as part of CLL14.**
Issue 7: Pre-progression off-treatment utility	

Which is the more plausible utility value for the 'pre-progression off treatment' health state: the company's base-case value of 0.82 derived from the company's submission for TA343, or the ERG's re-calculated value of 0.77 based on the gender-weighted, age-specific value of the general population?	**We would favour using 0.77 as I don't think extrapolation from TA343 is really appropriate.**
Issue 8: Quality of life impact of venetoclax with obinutuzumab	
Does the PFS benefit of VenG over GClb in previously untreated FCR or BR-unsuitable patients without del(17p)/*TP53* mutation translate into improved patient quality of life?	We are surprised that there is no significant QoL improvement in the VenG patient group as usually speed and depth of response- both of which were significantly in VenG's favour – usually lead to improved QoL unless the toxicity of a given arm is so much more than the other arm However, the toxicity data from CLL14 shows VenG to be highly tolerable. So we personally do not understand why in virtually all other studies where there are improvements in PFS/MRD, TTNT etc. that subsequently led to improved QoL it does not in this study. We would therefore question if the QoL aspects of CLL 14 - many differing countries involved, very small number of patients per centre etc- are truly informative and reflect what actually happened.

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia ID1402: ERG critique of the company response to Technical Engagement

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Declared competing interests of the authors

Dr Scott Marshall received sponsorship from AbbVie to attend educational conferences, and he has been paid to provide educational talks for clinicians and to attend advisory boards. He has no financial links or contracts with AbbVie. He has received similar payments/ sponsorship from most other pharmaceutical companies including Roche, Astrazeneca, BMS, Pfizer, Novartis, Celgene, Merck, Sanofi, Johnson & Johnson and Takeda.

Rider on responsibility for report

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1 SUMMARY

The objective of this report is to provide a critique of the company's response to the Technical Engagement (TE) for Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [ID1402].

The Evidence Review Group (ERG) critique responds to Issues 1 to 4 of the company's TE engagement response in the report below. The ERG has no further comments on Issues 5 to 8 of the company's TE engagement response.

2 Response to Issue 1: Patient population - part 1

Should patients with previously untreated CLL suitable for FCR or BR without del(17p)/*TP53* mutation be considered a relevant population for this appraisal?

In their response appendix, the company performed an indirect treatment comparison (ITC) to estimate hazard ratios (HR) for the relative efficacy of bendamustine with or without rituximab (BR) and fludarabine, cyclophosphamide and rituximab (FCR) on progression free survival (PFS) and overall survival (OS), using the studies identified in their literature search. This ITC compared venetoclax (Venclyxto) with obinutuzumab (VenG) (in unfit patients) with FCR/BR (in fit patients). The company incorrectly states that this was at the request of the ERG.

Note that the ERG has not checked for additional relevant trials. However, as noted in the ERG report we are aware of an ongoing trial in the 'fit' population: "the CS refers to an ongoing study of VenG. The CLL13 trial (NCT02950051) is a multi-centre four-arm RCT that has recruited 926 participants. The clinical trial record states the study is active and that the primary completion date is January 2023. The trial compares standard chemotherapy (FCR or BR) with VenG, venetoclax plus rituximab or triple therapy of VenG plus ibrutinib. The two co-primary outcomes are MRD negativity in peripheral blood and PFS. The population is previously untreated and meets the NICE scope, but does not meet the CS decision problem as participants are physically fit CLL patients (CrCl ≥70ml/min; CIRS ≤ 6; comorbidities excluded). The study is only including participants without del(17p) or TP53 mutation."

TE Appendix Table 2 describes criteria used by the company to categorise trial populations as fit or unfit based on criteria derived from the National Comprehensive Cancer Network

(NCCN) guidelines (unable to access) and clinical significance as determined by clinical experts at an AbbVie-organised Advisory Board. Although the ERG's clinical expert considers the criteria to be fair, they note that the upper limit of age for 'fit' varies and has increased over time. They consider that comorbidities, rather than age, is the main factor in determining fitness.

TE Appendix Table 2: Criteria for categorising patients as fit or unfit based on trial inclusion criteria

Category	Definition
Fit patients	Patients aged <65 years, with CIRS score <6
	Fludarabine eligible patients
Unfit patients	Patients aged ≥65 years
	Patients aged <65 years with CIRS score ≥6
	Patients that are specified to be fludarabine ineligible

Abbreviations: CIRS: cumulative illness rating scale.

The company does not discuss clinical heterogeneity of the trials or the appropriateness of combining the trials in an ITC. The ERG was unable to assess the characteristics of each study in the ITC in the limited time available, but has briefly summarised the CLL14 VenG trial and the four trials contributing to the FCR and BR comparator data below (the full network also included four additional trials). The ERG notes there is a high degree of variability in the eligibility criteria of the different trials. From the company's own assessment there is a high likelihood of characteristics varying across the trials given the differences in age and fitness, confounding any attempts at a robust analysis. The ERG considers that the populations of the trials violate the assumption of transitivity (no systematic differences between comparisons) for an ITC.

Furthermore, given that CLL patients often live for decades beyond their initial diagnosis, the duration of follow-up for each trial may also be influential, as differences in OS may take many years to separate.

CLL14 VenG trial

Presence of coexisting conditions with a total score ≥ 6 on the Cumulative Illness Rating Scale (CIRS) or a creatinine clearance of less than 70 ml per minute. Median age [redacted] years ([redacted]), [redacted] age 65 years or over. Categorised by the company as **'unfit'**.

ALLIANCE (ibrutinib, ibrutinib+rituximab, bendamustine + rituximab)
In patients age 65 years or older. Described in publication as characteristics 'typical of a population with untreated CLL'. Median age was 71 years (range 65 to 89). No information on comorbidities or fludarabine eligibility status, but eligible for bendamustine + rituximab. Categorised by the company as **'unfit'** on the basis of age.

MaBLe (bendamustine + rituximab, chlorambucil + rituximab)
Fludarabine-ineligible CLL patients. Judgment made by the investigator that the patients were not eligible for fludarabine, according to a set of pre-defined criteria based on the prescribing information for fludarabine at the time of study design; the CIRS was not used. Median age 72 years (range 38 to 91), 73% age 65 years or over. Categorised by the company as **'unfit'**.

CLL10 (bendamustine + rituximab, fludarabine + cyclophosphamide + rituximab)
Physically fit patients (CIRS <6, normal creatinine clearance ≤ 70 mL/min). Median age 62 years (range 54 to 69), 35% age 65 years or over. Categorised by the company as **'fit'**.

ECOG (ibrutinib + rituximab, fludarabine + cyclophosphamide + rituximab)
Reported as abstract only therefore limited details. Patients had to be aged less than 70 years and could be randomised to FCR therapy. No baseline characteristics. Categorised by the company as **'fit'**.

The ERG was unable to reproduce the company's Bayesian ITC in the time available, and implemented their own ITC in both R and Stata using a frequentist framework. The ERG requested the company's model and input, however the company only provided the model framework and not the input, so the ERG could not verify the accuracy of the company's ITC. Given the use of vague priors in the company's analysis, it was expected that the different approaches would give similar results. However, given the heavy influence of the survival extrapolations on the cost-effectiveness results, it is possible that even a small change in the magnitude of the HR could be meaningful.

The ERG included the hazard ratios from extended follow-up from RESONATE-2 and CLL14 in their analysis, and otherwise used the hazard ratios reported in the company's appendix, after verifying their accuracy.

Table 1 presents the estimated hazard ratios from the company's and ERG's ITCs alongside 95% confidence/credibility intervals. The wide confidence intervals associated with all estimates are immediately a concern given the reliance on these estimates for decision-making. This uncertainty, in addition to the ERG's other concerns with the NMA, should be carefully considered by the committee.

Table 1: Hazard ratios and 95% confidence intervals for ITC

Analysis source	PFS hazard ratio (BR vs VenG)	PFS hazard ratio (FCR vs VenG)	PFS hazard ratio (BR vs FCR)	OS hazard ratio (BR vs VenG)	OS hazard ratio (FCR vs VenG)	OS hazard ratio (FCR vs BR)
Company NMA	5.607 [3.201, 9.186]	3.873 [2.081, 6.613]	1.470 [1.142, 1.860]	1.263 [0.508, 2.648]	1.608 [0.559, 3.668]	1.204 [0.772, 1.996]
ERG NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 present estimates of hazard ratios from the company and ERG ITCs, alongside a series of sensitivity analyses performed on the ERG ITC which removed one key study to examine the impact on the ITC.

It is clear in Table 2 that the estimates are very sensitive to the choice of studies, and suggests that the estimates may not be robust. It reinforces the concern that such an analysis may be inappropriate given the known differences in baseline populations across all the trials.

Whilst the point estimates from the ERG and company analyses are in the middle of these estimates, the high variability present suggests the network should be considered inconsistent, another assumption necessary for a reliable ITC. It is questionable whether these results are at all informative of desired comparison, that is the relative efficacy of VenG, BR and FCR in a fit first-line CLL population. This is aligned with the company's own analysis of consistency, which shows considerable disagreement between the direct and indirect estimates from their ITC.

Table 2: Hazard Ratios from sensitivity analyses from the ERG ITC

Trial Excluded from NMA	PFS hazard ratio (BR vs VenG)	PFS hazard ratio (FCR vs VenG)	PFS hazard ratio (BR vs FCR)	OS hazard ratio (BR vs VenG)	OS hazard ratio (FCR vs VenG)	OS hazard ratio (FCR vs BR)
None (Company NMA)	5.607	3.873	1.470	1.263	1.608	1.204
None (ERG NMA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MaBLe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLL10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RESONATE 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed in Trial						
CLL10	-	-	1.626	-	-	1.034

Even if the hazard ratios could be considered reliable, there is still the question of the suitability of their use in the cost-effectiveness analysis. The hazard ratios will be based on data observed in the early stages follow-up and therefore it is impossible to know how long these effects are maintained. The hazard rates could increase, tend to 1, or even go against VenG in the future, however in this analysis the relative effects are assumed constant and remain for the full duration of the economic model.

Furthermore, the use of hazard ratios in a cost-effectiveness analysis should always be a last resort, when no other evidence is available, as in this case. There is a considerable loss of information when simplifying two arms of trial data down into a single hazard ratio, and many characteristics of the time-to-event data are lost. This effect is amplified across each trial included as the comparison from VenG to BR/FCR is made. Also, given that each comparison was only supported by a single trial, there is a risk that an over- or under-performing arm from any one trial would affect every other estimate in this ITC.

Finally, the company applies the hazard ratios onto the PFS and OS extrapolations for VenG patients from CLL14, who are not a fit population. Whilst this is not ideal, it is plausible that PFS may be relatively unaffected by the patient's general fitness. For PFS the ERG maintain their original extrapolation preferences (2-knot hazard spline model) over the company's preference (log-logistic).

The ERG perceived that for OS, the fitness of patients was likely to have a bigger impact than for PFS. However, the company's extrapolation of VenG OS is heavily reliant on background mortality, which the ERG previously criticised for being too optimistic for the unfit population given the associated comorbidities. The ERG acknowledges that it is plausible this extrapolation may be more suitable for the fit population and do not have a better alternative. Hence the company's OS extrapolation is maintained.

For their base-case, the ERG prefers to use the estimates from their own ITC rather than the company's ITC, though understand that neither analysis could be considered reliable given the discussed issues.

Whilst for PFS, there was a statistically significant difference between VenG and BR/FCR, this was not the case for OS. Hence, the ERG considers a scenario assuming equal OS for the three treatments in a scenario analysis. The impact of this on the cost-effectiveness results is presented in Issue 1: Sensitivity analyses - see Table 5.

The economic model submitted alongside the company's response to TE Issue 1 is based on the model presented for the comparisons VenG vs. GClb and VenG vs. Ibrutinib in the 'unfit' CLL population. Inputs in this economic analysis are based on the company's NICE addendum model, as opposed to the ERG model.

Limited modifications were made beyond changes in the clinical effective parameters. These included the necessary addition of treatment costs for medications that make up BR and FCR (fludarabine cyclophosphamide, sourced from the British National Formulary and bendamustine sourced from the eMIT national database) and a change to probabilities of adverse events related to FCR and BR (sourced from the literature).

No changes were made in health state utility values; these were the values used in the company's addendum. The values relate to the following states: PFS on intravenous treatment (0.67), PFS off treatment (0.82), PFS on oral treatment (0.71) and PPS (0.6). The same health state utility values were applied to all comparators. As noted in the ERG report, these values, which have been previously used in the economic model submitted as part of TA343, were obtained from a utility elicitation study carried out with members of the general public in the UK. In the previous submission, the ERG questioned the value used for the 'PFS, off treatment' state (0.82) as unrealistically high and, although the company accepted the ERG's proposed

value of 0.7703, this value has not been used in the submitted model. Simple sensitivity analyses carried out by the ERG to explore the impact of higher utility values due to a fit population resulted in a small change in ICER values, but not a change in direction (see Scenario 2 in Table 6 in Issue 1: Sensitivity analyses).

Subsequent treatment costs were calculated on the basis that first line treatment with either VenG, FCR or BR is followed by treatment with venetoclax and rituximab or ibrutinib. The ERG's clinical expert confirmed that this is reflective of clinical practice. In the absence of robust evidence base, the company has taken a conservative approach in modelling subsequent costs for BR and FCR. This has resulted in substantially lower subsequent treatment costs for these comparators.

The generated results reflected the company's preferred base-case analysis, without taking into account any amendments suggested by the ERG (e.g. utility value for the 'progression-free, off-treatment' health state, ERG's preferred PFS, TTnT and OS extrapolations).

The base-case deterministic cost-effectiveness results (at list price for all comparators) are given in Table 3 below (Table 16 in the company's TE response appendix).

Table 3. Company's base case results at list prices (deterministic)

Treatment	Total costs, £	Total QALYs	Incremental costs, £ (versus VenG)	Incremental QALYs (versus VenG)	ICER, £/QALY (versus VenG)
FCR	[redacted]	5.585	[redacted]	2.066	[redacted]
BR	[redacted]	5.931	[redacted]	1.720	[redacted]
VenG	[redacted]	7.651			

Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

The analyses carried out by the ERG described above led to the following ERG preferred base-case amendments:

- Change in the utility value for the 'progression-free, off treatment' state.
- PFS extrapolation changed from log-logistic to hazard spline (2 knot) and changes in mean HR for PFS.
- Change in the HR for OS.

The changes and their implementation in the model are given at the end of this document.

Results with the ERG suggested changes are presented in Table 4 below.

Table 4. ERG base case results at list prices (deterministic)

Treatment	Total costs, £	Total QALYs	Incremental costs, £ (versus VenG)	Incremental QALYs (versus VenG)	ICER, £/QALY (versus VenG)
FCR	[redacted]	5.489	[redacted]	1.356	[redacted]
BR	[redacted]	5.984	[redacted]	0.860	[redacted]
VenG	[redacted]	6.845			

Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Issue 1: Sensitivity analyses

Results of ERG's sensitivity analysis to explore the impact of changes in OS HR and utility values are presented below.

Table 5. Sensitivity analysis of OS HR=1 between VenG and FCR and BR.

Treatment	Total costs, £	Total QALYs	Incremental costs, £ (versus VenG)	Incremental QALYs (versus VenG)	ICER, £/QALY (versus VenG)
FCR	[redacted]	6.629	[redacted]	1.021	[redacted]
BR	[redacted]	6.438	[redacted]	1.213	[redacted]
VenG	[redacted]	7.651			

Abbreviations: BR: bendamustine with rituximab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab.

Table 6. Sensitivity analyses to explore impact of changes in utility values.

Scenarios	Health state				Cost-effectiveness results	
	PFS, on IV treatment	PFS, off treatment	PFS, on oral treatment	PPS	ICER (£ per QALY, VenG vs FCR)	ICER (£ per QALY, VenG vs BR)
Company's base case values in addendum and new model	0.670	0.820	0.710	0.600	[redacted]	[redacted]
Scenario 1. Company's base case and ERG's preferred value for 'PFS, off treatment' state	0.670	0.770	0.710	0.600	[redacted]	[redacted]
Scenario 2. Scenario 1 values +10%	0.737	0.847	0.781	0.660	[redacted]	[redacted]
Scenario 2. Scenario 1 values -10%	0.603	0.693	0.639	0.540	[redacted]	[redacted]

Abbreviations: BR: bendamustine with rituximab; FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenG: venetoclax with obinutuzumab.

Issue 1. Sensitivity analyses - ERG's changes in the model

Utility value for 'progression-free, off treatment' state.

- On sheet 'Utilities', cell F20, replace the current value (0.820) by 0.770253956

PFS

- On sheet 'Survival', change cells E15 and E16 extrapolation from "Log-logistic" to "Hazards spline (2 knot)"
- On the sheet 'NMA', change cell AA10 to 3.551, and cell AB10 to 5.189.

OS

- On the sheet 'NMA', change cell AG10 to 1.526, and cell AH10 to 1.165.

3 Response to Issue 1: Patient population - part 2

Is the patient population in the CLL14 trial appropriate for decision-making, particularly in the company's subgroup without a del(17p)/TP53 mutation?

The company states "The technical report incorrectly states that "*the entire CLL14 trial population (which included patients with and without del(17p)/TP53 mutation) was used as evidence for the subpopulation without del(17p)/TP53 mutation*"."

The ERG notes that the technical report is correct for the evidence of clinical effectiveness.

4 Response to Issue 2: The most plausible PFS extrapolation: Non-del(17p)/TP53-mutated population

In general, the company's response to Issue 2 contains considerably selective statistics which consistently fail to provide a clear and fair comparison between the ERG and company preferred curves.

The ERG maintains that the long-term estimates from the company's PFS extrapolation are too optimistic, and are inconsistent with the views of the ERG's clinical expert. The company's estimate of mean PFS is also inconsistent with the corresponding estimate from TA343.

The ERG's preferred curve produces an estimate of mean PFS that is more consistent than the company's to those from TA343, the appraisal of GClb. It is also the only curve which aligned with the views of the ERG's own clinical expert. It is unfortunate that the ERG's modelling of PFS does not line up with the company's own clinical advisors.

The ERG has checked the company's claim that the ERG's base-case is influenced at the same point in time by background mortality as the company's base-case, and this appears to be factually inaccurate. The ERG understand that the hazard rate of the 2 knot hazard spline is always greater than the hazard rate of background mortality, but welcome evidence from the company which supports the contrary. Meanwhile, the company's PFS curves are modelled by background mortality from roughly [redacted] years and [redacted] years through the 30-year time horizon.

Hence, the ERG believes their preferred PFS curve offers clear improvement over the company's selection.

5 Response to Issue 3: The most plausible OS extrapolation: Non-del(17p)/TP53-mutated population

The ERG maintains their view that the company's preferred extrapolation of OS is implausibly optimistic.

To accept the company's analysis would mean concluding that neither the presence of CLL or the comorbidities that have led to the inclusion of patients in CLL14 negatively affect their background mortality rate compared to the age matched UK population.

The ERG and their clinical expert do not consider this conclusion to be plausible, and presented an alternative approach to modelling OS, one that did not rely on background mortality from roughly 5 years to predict patient survival.

The company are critical of the ERIC study used in the ERG approach, stating four reasons that ERIC may not be suitable: ERIC is not a clinical trial, VenR was not available at relapse, Clb dosage was different to CLL14, and that ERIC lacked UK centres.

These arguments presented by the company are weak, for the following reasons.

Firstly, whilst clinical trial evidence is the gold standard for comparing two interventions, real world evidence is favourable when aiming to estimating efficacy in a real world population. A trial population will typically not contain the heterogeneity of a real world population, and the trial participants may have a difference healthcare experience. Furthermore, when data are as immature as the OS data from CLL14, extrapolations should not be relied upon to provide an accurate prediction, and external sources must be utilised where available.

Secondly, the ERG acknowledges it is unlikely that VenR was received by patients in the ERIC study, however there is insufficient published evidence to draw conclusions over the efficacy VenR has on OS, especially after first line venetoclax therapy. The immaturity of the CLL14 data means it is unlikely to capture the potential influence of later lines of therapy.

Thirdly, the dosing and treatment intensity reported in the ERIC study may be more representative of UK practice than CLL14. The company fails to consider which might better represent UK care, and only compares the two studies.

Fourthly, whilst the ERIC study may not contain any UK patients, CLL14 is also at high risk of failing to be representative of UK practice since it contains only 8 UK patients.

Furthermore, the ERG could not identify the evidence to support that 100% of VenR patients who later received ibrutinib achieved a response, using the referenced source from the company. Using the same reference, the ERG note that only 2 of 14 first-line VenR patients responded to subsequent venetoclax therapy, though 10 of these were unevaluable.

In the absence of other alternatives, the ERG modelled the CLL14 data for 3 years and then used extrapolations based on the ERIC study. The ERG approach combines the observed data from CLL14 with the extended follow-up from the ERIC study, with background mortality coming into effect from 15 years. There is considerable uncertainty around the potential influence of later lines of therapy on OS, however the ERG maintain that their approach offers at the very least, a plausible alternative to the company's analysis.

6 Response to Issue 4: Subsequent treatment costs

Is it appropriate to assume that subsequent treatment costs apply from the initiation of second-line treatment until death within the economic model?

The ERG welcomes the company's decision to engage in addressing the issue that, in the addendum model, costs of subsequent treatment were applied until death, disregarding the fact that patients may have discontinued treatment.

Ideally, a comprehensive analysis would model the costs of subsequent treatment according to rigorous estimates of when patients start such treatments, how long they stay on each treatment and what gaps there may be between alternative subsequent line treatments. The ERG noted the absence of rigorous information on these parameters, but pointed to available indications in the literature, which were used in company's submission.

We believe that adopting a conservative approach, which places limits to the number of treatment cycles in accordance with estimates in the published literature and applies treatment costs to incident patients, is preferable to the modelling approach in the company's addendum model.

Thus, the ERG welcomes the company's amendment and considers this as a more appropriate representation of the costs of subsequent treatments.