NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Final Appraisal Determination Document

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - AbbVie - letter, comments & new evidence appendix (company)
   - British Society of Haematology - Royal College of Pathologists (joint response)
   - Chronic Lymphocytic Leukaemia Support Association - Lymphoma Action (joint response)
   - Leukaemia CARE
   - UK Chronic Lymphocytic Leukaemia Forum
   - Gilead sciences
   - Janssen-Cilag

   'No comment' response from Department of Health & Social Care

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Peter Hillmen – Clinical expert - nominated by AbbVie

   Comments on the Appraisal Consultation Document received through the NICE website - *None*

4. **Addendum of new evidence** – submitted by AbbVie

5. **Evidence Review Group documents** - prepared by Warwick Evidence**:**
   - Critique of company new evidence
   - Critique of company addendum
   - Updated ERG base case model with warning effect

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	BSH-RCPath	It is fair to say that the committee has considered all the evidence presented in front of them.	Comment noted. No action required.
2	Consultee	BSH-RCPath	However, the recommendation implies that venetoclax with rituximab in the relapsed and refractory CLL is not an effective treatment option for this group of patients as compared to other available options. There is a clear benefit demonstrated in terms of deeper responses and progression-free survival as compared to chemo-immunotherapy arm based on the short follow-up and this has been recognised by the committee.	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status and it concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
3	Consultee	BSH-RCPath	Comparison with B-cell receptor antagonist therapy is nearly impossible to make due to two reasons: One is the different mechanism of action of the drugs resulting in variable responses. B-cell receptor antagonist including ibrutinib and idelalisib invariantly result in partial responses in majority with only few patients achieving complete responses. MRD negativity is not achievable with this group of drugs. On the other hand, Venetoclax with rituximab achieves deeper remissions as well as MRD negativity. This make it very difficult to compare the two classes of drugs other than in a head to head comparison in a trial (Unlikely to happen). Secondly is the variation in the phase 3 trial population of various included studies that is manifested in the varied results of clinical and cost-effectiveness analysis. Hence, conclusions to draw degree of effectiveness or ineffectiveness with fixed therapy versus continuous therapy is very difficult.	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status and it concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
4	Consultee	BSH-RCPath	It is a very sensible to review the data cut off at the later time point once	Comment noted. The committee discussed the

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			patients have finished 2 years of venetoclax to establish the continued effectiveness of the treatment and we would agree with that entirely. The depth of response does matter in all venetoclax studies including Phase 1b venetoclax with rituximab study (Seymour et al) where patients achieving complete response and MRD negativity translated in longer disease-free relapse. If the later data cut-off suggests continued deep responses and very few relapses, it is hard to justify why this fixed duration therapy would not be beneficial to the patients.	new evidence based on the updated data cut which had a median follow-up of 36 months and concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
5	Consultee	BSH-RCPath	As with any CLL study, the overall survival data will take time to mature and there are salvage treatments available especially in the chemoimmunotherapy arm which makes it difficult to make a short-term decision.	Comment noted. No action required.
6	Consultee	BSH-RCPath	The economic analysis should be again considered based on the later cut-off data in order to make a better judgement on the continued effectiveness of the treatment and we would agree with that.	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4) and a cost-effective use of NHS resources, therefore it recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
7	Consultee	BSH-RCPath	We would ask the committee to review the recommendation based on various points raised. This treatment opens a choice for our patients and gives us flexibility to treat our patients with a very effective treatment which does not at least appear inferior to other options available at present.	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
8	Consultee	BSH-RCPath	If NICE wants to wait for the data to mature then provision of this option on Cancer drug fund would be sensible which will allow us to accumulate real world data as well and may help in future recommendations.	Comment noted. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic

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				lymphocytic leukaemia in adults (see FAD section 3.17).
9	Consultee	CLLSA-LA	We request that the updated and most recent clinical evidence from Prof Dr P Hillmen, that he offered at the Appraisal meeting, is fully considered as part of the appraisal consultation.	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4) and a cost-effective use of NHS resources, therefore it recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
10	Consultee	CLLSA-LA	Equality issues will arise if Venetoclax plus Rituximab is not available for first relapsed patients. Restricting the target population to patients post chemo-immunotherapy excludes patients with del17p, TP53 mutation and those that were treated in a clinical trial (particularly FLAIR) who received Ibrutinib as first line treatment. Venetoclax plus Rituximab is a very important and effective treatment option for this group who have few treatment options and consequently a poor prognosis.	Comment noted. In accordance with the Guide to the methods of technology appraisal 2013 section 6.1.12, for this topic the appraisal committee made recommendations regarding the use of venetoclax with rituximab within the terms of its UK marketing authorisation.
11	Consultee	CLLSA-LA	Due to the heterogeneous nature of the disease and the age range of patients, there is a need for access to multiple treatment options for relapsed/refractory patients with CLL. For relapsed patients with comorbidities, which may restrict their treatment options, Venetoclax plus Rituximab is a valuable and important effective option.	Comment noted. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
12	Consultee	CLLSA-LA	A fixed duration of treatment is both acceptable and welcome to CLL patients.	Comment noted. The committee acknowledged the patient expert comment about patients welcoming a fixed treatment duration (see FAD section 3.3).
13	Consultee	CLLSA-LA	Venetoclax plus Rituximab offers increased remission rates with the potential of MRD negativity and hopefully prolonged survival with an acceptable safety profile.	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual

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			This is a substantial shift for the prognosis of relapsed CLL patients.	disease status. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17).
14	Consultee	Leukaemia Care	We thank the committee for the opportunity to respond	Comment noted. No action required.
15	Consultee	Leukaemia Care	Decision by Appraisal Committee to not recommend venetoclax plus rituximab. We are concerned about potential delays preventing patients and clinicians from accessing this treatment and do not agree with the ACD non-recommendation 1.1 of Venetoclax with rituximab use within its anticipated marketing authorisation, for treating relapsed or refractory chronic lymphocytic leukaemia in adults. European Commission approval was granted on 1st November for the use of this novel combination in this setting across all 28-member European states, Iceland, Liechtenstein and Norway. Additional data is now available providing 36 month follow up data in the ASH Murano study abstract publication https://ash.confex.com/ash/2018/webprogram/Paper118012.html The full study paper should be available to the ERG and committee from the company and will published publicly in early December at ASH 2018.	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4) and a cost-effective use of NHS resources, therefore it recommended venetoclax with rituximab (See FAD section 3.17).
16	Consultee	Leukaemia Care	Treatment choice. CLL is a complex and varied disease. Most patients are in an older group living with many comorbidities which make current treatments unsuitable or intolerable. Repeated chemotherapy is not generally recommended today due to cumulative toxic side effects, intolerance or unsuitability. Today Ibrutinib is the current clinical standard of care for treating R/R patients and idelalisin plus rituximab as an alternative. Ibrutinib or idelalisib plus rituximab are associated with side effects that can exclude their use in a high proportion of R/R patients or are hard to tolerate by many over time. Venetoclax + rituximab has a favourable tolerability and toxicity profile and gives patients with comorbid, cardiac, anticoagulation and bowel issues an alternative to treatment with Ibrutinib or the alternative of idelalisib plus rituximab. Clinical choice is critical for clinicians to be able to tailor therapy and long-	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended venetoclax with rituximab (See FAD section 3.17).

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			term treatment plans to the individual's health needs thereby ensuring survival and quality of life is maximised. Patients understand the limitations of therapies available as standard of care in this setting and that they do not come without serious risk of complication or long-term side effects. This is causing some considerable distress to many in this setting.	
17	Consultee	Leukaemia Care	Treatment sequencing and personal treatment plans. In an era of developing personalised medicine CLL patients are becoming increasingly aware of the need for an appropriate tailored approach to their own treatment, rather than the dangers associated with a one size fits all approach. Patients and their clinicians require treatment options to fit with the increasingly complicated treatment landscape and treatment sequencing complexities, to ensure treatment continuity. Patients relapsing from a prior therapy require access to tolerable therapies that offer a chance of reaching MRD negativity early, followed by a treatment free period and improved quality of life. Patients worry they will not achieve enduring remissions or worry about side effects or toxicities of currently available options	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17).
18	Consultee	Leukaemia Care	Important new treatment option 3.1. We are pleased the committee concluded that venetoclax plus rituximab could be an important treatment option for people with relapsed or refractory chronic lymphocytic leukaemia and pleased that 36 month cut off data confirms the durability of responses to this therapy.	Comment noted. No action required.
19	Consultee	Leukaemia Care	Clinical effectiveness. We are pleased the committee concluded that the clinical-effectiveness 3.3, 3.4 was relevant to NHS clinical practice in England. At 23.8 months of venetoclax treatment about 60% of patients in the trial had negative minimal residual disease status, which is "a strong predictor of lasting remission in patients with chronic lymphocytic leukaemia". We are pleased to see that 36 month data shows few patients progressing after the 2-year therapy.	Comment noted. No action required.
20	Consultee	Leukaemia Care	Suitability for Cancer Drugs Fund. We are very concerned that early access to this urgently needed treatment is being delayed and do not agree with the ACD conclusion and reasoning 3.16 that venetoclax plus	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months and

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			rituximab is not suitable for the Cancer Drugs Fund. We are hopeful that the company will ensure that they have now properly addressed the ERG, appraisal committee and NHSE concerns. We hope 36 month trial cut off data analysis will enable use of correct hazard ratios in modelling to reflect the fixed duration of venetoclax treatment. Early access through the Cancer Drugs Fund will help meet an urgent area of unmet need and fill a therapeutic void for relapsed patients.	concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). The committee recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17).
21	Consultee	Leukaemia Care	Loss of treatment effect. We understand that potential loss of treatment effect after 2 years with venetoclax plus rituximab was not reflected in the original analysis. 3.10 However we are pleased that recently published 36 months cut off data enables modelling to be created that will reduce uncertainties that arose from the original modelling at 23.8 months. This should now strengthen modelling extrapolations, making ICER calculations more robust. We are hopeful that this latest available data will enable the company and ERG to remodel comparisons and data to effectively satisfy requirements for CDF inclusion.	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months and concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17).
22	Consultee	Leukaemia Care	Additional treatment benefits. We are concerned that the committee believes that there are no additional benefits that are not captured in the cost-effectiveness analysis, despite expressing the belief that the new treatment is beneficial for patients. 3.14. Patient groups have presented feedback of patient experience with the treatment and outcome improvements. We believe that making this treatment available via the CDF will enable uncertainties to be addressed and patient reported outcomes to be collected, strengthening the data on the benefits to patient quality of life.	Comment noted. The committee recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17).
23	Consultee	Leukaemia Care	Treatment step change and innovation. Venetoclax plus rituximab offers a step change in treatment strategy. Venetoclax plus rituximab gives patients a chance of a achieving a preferred treatment break, and enduring remission, without the complications and side effects caused by a continuous therapy or very myelotoxic chemoimmunotherapy (CIT). Many cannot tolerate or are not suitable for retreatment with a CIT or with continuous therapies such as ibrutinib & idelalisib plus rituximab, due to comorbidities and side effects associated with these current standards of	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended venetoclax with rituximab for routine

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			care.	commissioning (See FAD section 3.17).
24	Consultee	Leukaemia Care	Patient experience. In our CLL patient experience survey, patients were asked, 'Would you consider it positive if a treatment plan contained a treatment-free period or included stopping treatment altogether ?'– analysis of responses confirms that patients prefer a treatment-free period or prefer being able to stop treatment altogether. Venetoclax plus rituximab provides a treatment free interval after a defined 2-year treatment period, the majority are achieving MRD negativity and are still in remission at 36months.	Comment noted. The committee acknowledged the patient expert comment about patients welcoming fixed treatment duration (see FAD section 3.3). It recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17)
25	Consultee	Leukaemia Care	Health economics. We believe that venetoclax plus rituximab as a 2-year limited treatment therapy has plausible potential to be cost-effective versus the current standard of care. More recent trial data when used in health economic evaluations confirms favourable ICER rates for Ven+R compared to comparators. We request the committee reconsider their original decision and make this treatment available through the Cancer Drugs Fund. Continued data collection through CDF will remove uncertainties without denying patients in the relapsed setting an effective therapy approved for European prescribing.	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). The committee recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17)
26	Consultee	UK CLL	Evidence of the (non)-efficacy and toxicity of retreatment with chemoimmunotherapy in previously treated CLL patients I refer to our review of this option from August of this year following the TIMES letter regarding access to Ibrutinib for patients relapsing within three years of chemoimmunotherapy. As a result of this option appraisal, NHSE accepted the evidence against repeat CIT at relapse and changed the Bluetec inclusion criteria in favour of Ibrutinib. Retreatment with BR The first study evaluating Bendamustine and Rituximab systematically for the treatment of relapsed CLL showed a median PFS of 15.2 months for BR at 24 months follow-up1. At the time, Ibrutinib was not available and therefore the study included patients with fludarabine-refractory CLL and also patients with deletions of chromosome 17p. Toxicities were mainly haematological and affected 25% of patients overall.	Comment noted. No action required.

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			The Helios study compared Ibrutinib with bendamustine and rituximab with placebo, bendamustine and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma2. Patients who had relapsed early after chemoimmunotherapy (i.e. within two years) were excluded. 48% of patients recruited had received only one prior line of therapy. In addition, patients had to be fit enough to tolerate further chemoimmunotherapy with BR. With a median follow-up of 17 months, the median PFS for Ibrutinib (plus BR) treated patients was not reached compared to 13.3 months for those treated with BR only. At 18 months, 79% of patients in the Ibrutinib treated group had not relapsed versus 24% of patients treated with BR. The most common Grade 3 or 4 side-effects were neutropenia and thrombocytopenia. These occurred in about 50% of patients in both arms and were attributed to BR. Infections were seen in about 10% of patients in both arms. These data confirm the results from the Murano study3 that had very similar inclusion/exclusion criteria to Helios and recruited mostly patients who had only one prior line of therapy and showed a median PFS of 17 months for BR-treated patients. The risk of Grade 3 or 4 neutropenia was 51 and 39% for Helios and Murano, respectively. Importantly, bendamustine was withdrawn from the CDF for relapsed CLL when Ibrutinib was NICE approved in 2016. Re-treatment with FCR or other multi-agent chemoimmunotherapy The LUCID study4 used FCR as the control arm. 62% of patients recruited had undergone only one prior line of therapy, 58% had received fludarabine containing regimen, the others had received less effective chemotherapy or chemoimmunotherapy. The median PFS of the FCR treated control cohort was 24 months. 40% of patients had a serious adverse event, mainly due to infection related hospital admissions. 5% of patients died and the discontinuation rate was 30%. Together, these data clearly indicate that FCR in the relapsed setting lacks efficacy and has significant toxicity. The REACH study5 compared FC against FCR. Patients with prior exposure to FCR were excluded. Despite that, the PFS of FCR treated	

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			patients was only 30 months. Importantly, 89% of patients presented with Grade3 or 4 neutropenia and the treatment-related death rate was 7%. Neiderle et al compared BR and FCR in patients relapsing after frontline therapy with alkylating agents6. Patients who had received prior treatment with bendamustine or fludarabine were excluded. Despite this, the PFS was less than two years in both arms and not statistically different between the two arms. Other studies evaluating multi-agent chemoimmunotherapy in the relapsed setting are the MDACC single centre observational study7 and the French Collaborative groups8. Both included patients with prior exposure to FCR. Re-treatment regimen were more heterogenous (FCR, BR, alemtuzumab, CHOP-R etc), but the median PFS was under 2 years1,7,9. Importantly, multiagent chemoimmunotherapy, in particular FCR is associated with an increased risk of second cancers and AML. In the largest series reported, the risk of second cancers was 2.38 times higher than the expected risk in the general population. The rates for t-AML/MDS (5.1%) was also high10. Up until now, the evidence in favour of using the targeted agents (Ibrutinib, Idelalisib, Venetoclax) instead of CIT in the relapsed setting - although compelling- , has been based on “across trial” comparisons (see above). The Murano study is the first to compare a targeted agent directly against current best available chemoimmunotherapy. References 1. Fischer, K. et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A Multicenter Phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J. Clin. Oncol. 29, 3559–3566 (2011). 2. Chanan-Khan, A. et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet	

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			Oncol. 1–12 (2015). doi:10.1016/S1470-2045(15)00465-9 3. Seymour, J. F. et al. Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N. Engl. J. Med. 378, 1107–1120 (2018). 4. Awan, F. T. et al. A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed ch. Br. J. Haematol. 167, 466–477 (2014). 5. Robak, T. et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J. Clin. Oncol. 28, 1756–1765 (2010). 6. Niederle, N. et al. Bendamustine compared to fludarabine as second-line treatment in chronic lymphocytic leukemia. Ann. Hematol. 92, 653–660 (2013). 7. Tam, C. S. et al. Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). Blood 124, (2014). 8. Fornecker, L. M. et al. Salvage outcomes in patients with first relapse after fludarabine, cyclophosphamide, and rituximab for chronic lymphocytic leukemia: The French intergroup experience. Am. J. Hematol. (2015). doi:10.1002/ajh.23999 9. Badoux, X. C. et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood (2011). doi:10.1182/blood-2010-08-304683 10. Benjamini, O. et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. Leuk. Lymphoma (2015). doi:10.3109/10428194.2014.957203	
27	Consultee	UKCLL	Treatment with Ibrutinib or Idelalisib: a One-size-fits-all-model for patients with relapsed CLL is dangerous	Comment noted. The committee discussed the new evidence based on the updated data cut

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			One of the arguments currently used in the TA is that Ibrutinib and Idelalisib are already NICE approved for patients with relapsed CLL and that it is not clear what the VR combination would add. We refer to the MHRA routine European review that examined the safety profile of ibrutinib (https://www.gov.uk/drug-safety-update/ibrutinib-imbruvica-reports-of-ventricular-tachyarrhythmia-risk-of-hepatitis-b-reactivation-and-of-opportunistic-infections). In this meta-analysis of all Ibrutinib trials, an excess death rate due to cardiac toxicities was found in addition to an increased risk of hepatitis B reactivation and a significant risk for opportunistic infections. As a result, the MHRA asked the company to update the patient information and to include: ventricular tachyarrhythmia including sudden cardiac death as a common adverse reaction (<10 in 100 patients) hepatitis B virus reactivation as an uncommon adverse reaction Importantly, clinicians were advised to withhold Ibrutinib in patients with symptoms that could be due to arrhythmia, and patients who are particularly vulnerable to opportunistic infections, such as patients with pre-existing lung disease, should be considered for alternative therapies and started on prophylaxis. In addition to these life-threatening complications, 16% of patients on Ibrutinib will develop atrial fibrillation and need anticoagulation with NOACs (warfarin is contra-indicated) further adding to co-morbidities and cost of CLL treatment. Idelalisib The committee is aware of the increased risk of immunogenic side-effects relating to PI3K inhibitors such as Idelalisib with 20% of patients developing treatment-related colitis or pneumonitis that leads to permanent discontinuation of therapy. Idelalisib use is therefore restricted to patients who are intolerant to Ibrutinib. However, the number of patients intolerant to both drugs is increasing as we begin to learn more about the long-term side-effects of Ibrutinib. Venetoclax &Rituximab	which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17)

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			The Murano study shows that the VR combination is safe and well tolerated and would therefore represent a significant step-change in the choice of therapies available for our patients, especially for the significant number of patients with a previous history of cardiac or pulmonary disease. The VR combination achieves an unprecedented rate of MRD negativity convincingly showing its superiority with respect to efficacy compared to CIT. Moreover, patients find the fixed duration of therapy highly attractive. Importantly, patients with treatment-naïve TP53-disrupted CLL should also have a choice (ibrutinib or venetoclax & rituximab), and patients with relapsed TP53-disrupted CLL should be given access to the same (superior) treatment of venetoclax in combination with rituximab instead of venetoclax only (current treatment) as the TP53 wildtype patients. Finally, we note the committee is concerned there may be loss of treatment effect after 2 years of VR when treatment is discontinued. However, we note that the latest MURANO data to be presented at ASH 2018 in 2 weeks from now is not suggestive of such a loss of effect, as the PFS in the latest analysis in patients who completed 2 years of treatment remains excellent at 92% and 87% at 6 and 12 months respectively. This implies continued remissions in patients off treatment.	
28	Consultee	AbbVie	AbbVie is pleased to confirm that with all patients off treatment and with a median of 3 years of follow-up, compelling efficacy results continue to be observed with VEN+R in addition to a safety profile that continues to be manageable, predictable and consistent with the known safety profile of both agents. The rate of CLL progression in the first 12 months after venetoclax completion was modest (13%), supporting the feasibility and safety of a time-limited duration of VEN+R. The median PFS in the VEN+R arm was not reached (55 events of progression or death in 194 patients; 28.4%). The median PFS in the BR arm was 17.0 months (144 events in 195 patients; 73.8%) (95% CI: 15.7, 21.7). There were no new safety signals. The prognostic significance of achieving undetectable	Comment noted. The committee discussed the new evidence based on the updated data cut which had a median follow-up of 36 months. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended it for routine commissioning as an option for treating relapsed or refractory chronic lymphocytic leukaemia in adults (see FAD section 3.17)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			MRD is well established: it leads to longer periods of remission and survival. A higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at completion of venetoclax treatment (i.e. month 24) in the VEN+R arm (48% uMRD) vs the BR arm (2% uMRD). Furthermore, VEN+R pts who achieved uMRD had durable PFS, thus providing biological plausibility for continued treatment benefit post the 2 year fixed treatment duration of VEN+R. AbbVie welcomes the opportunity to address the committee's questions using the results of the recent data cut from the MURANO trial and has provided additional analyses in Appendix 1. The main conclusion from these analyses is that VEN+R dominates ibrutinib and the probability that VEN+R is cost-effective compared with ibrutinib at £20,000 per QALY is 100% in both the list and net price comparisons. AbbVie acknowledges the uncertainties in the relative efficacy estimates based on the MAIC and has provided substantial evidence of a robust ICER (i.e. VEN+R dominates Ibrutinib) on which the committee can decide whether there is plausible potential for VEN+R to be cost-effective. Therefore VEN+R meets the criteria to be included in the CDF. AbbVie would welcome a CDF recommendation and anticipates that longer term follow-on data from the MURANO trial will reduce uncertainties in clinical and cost-effectiveness results.	
29	Consultee	AbbVie	Page 7 (3.5) states: "The ERG also noted that patients had not been matched correctly, making the population in the RESONATE trial (ibrutinib) appear healthier than the population in the MURANO trial (venetoclax plus rituximab). This meant that the benefit of ibrutinib may have been underestimated" This is factually inaccurate since the individual patient data came from the MURANO trial. The approach we took was to match the MURANO patient population to reflect the RESONATE patient population. Therefore, we made the MURANO population less healthy to match that of RESONATE, rather than the	Thank you for your comment. This has been deleted from the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			RESONATE population better off. Please also refer to page 47 of the ERG report	
30	Consultee	AbbVie	The ACD makes a number of statements suggesting that AbbVie's submission and economic model did not account for the 2 year fixed treatment duration of venetoclax in combination with rituximab – specifically not reflecting a change in treatment effect after 2 years. This is factually inaccurate and potentially misleading as Table 67, page 165 of the NICE submission includes a description of waning scenarios whereby the VEN+R treatment effect following treatment discontinuation is explored.	Comment noted. We acknowledge that it was not clear in the ACD that it was the base case analysis that did not include the diminishing treatment effect after venetoclax treatment was stopped at 2 years. The 2 year waning effect was presented at the second committee meeting and sections 3.10 and 3.12 of the FAD have been updated.
31	Consultee	AbbVie	Page 3 states: "There are problems with the economic model inputs. For example, there are inconsistencies between the clinical- and cost-effectiveness data used because the costs of venetoclax treatment last for 2 years but the benefits continue for more than 2 year" The statement is potentially misleading. This is not an inconsistency – this is an assumption in the model based on clinical data and clinical expert opinion supporting ongoing treatment benefit beyond the 2 year fixed treatment duration. The prognostic significance of achieving uMRD is well established: it leads to longer periods of remission and survival. Supportive information was presented in the NICE submission: a higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at the end of combination therapy (EOCT) in the VEN+R arm vs BR arm (62% for VEN+R vs 13% for BR). The recent data cut confirms that this pattern was maintained at completion of treatment (i.e. at 24 months): 48% uMRD in the VEN+R arm vs 2% uMRD in the BR arm. Furthermore, VEN+R pts who achieved uMRD had durable PFS, thus providing biological plausibility for continued treatment benefit post the 2 year fixed treatment duration of VEN+R. Moreover, this is not unprecedented in CLL as fixed treatment duration combinations such as FCR have demonstrated long remissions. (Kirsten Fischer et al (2016)"Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial." Blood 127, no. 2 (2016): 208-215)	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4). It recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
32	Consultee	AbbVie	Pages 7 and 8, Section 3.5 states: "The committee noted that the MAIC had not been adjusted to account for the fixed treatment duration of venetoclax, which may have resulted in a greater treatment benefit for venetoclax plus rituximab". This is then used as justification for stating: "The committee agreed that the MAIC was flawed". This is factually inaccurate and potentially misleading. The fixed treatment duration of venetoclax is not a variable that can be adjusted for in population-adjusted indirect comparisons. Section 3.9, which repeats this factual inaccuracy should also be amended. Please also refer to comments 3 and 4 above.	Thank you for your comment. This has been amended in section 3.5 of the FAD.
33	Consultee	AbbVie	Page 3, last paragraph and Page 11 (3.13) states: "Estimates ranged widely from venetoclax plus rituximab being less costly and more effective to venetoclax plus rituximab being less costly and less effective when compared with ibrutinib plus rituximab" Please delete plus rituximab as the comparison is with ibrutinib monotherapy and not Ibrutinib with rituximab	Thank you for your comment. This has been amended in section 1 of the FAD.
34			Page 8 (3.17) states "The clinical experts explained that venetoclax plus rituximab is occasionally associated with tumour lysis syndrome. This can cause a rapid breakdown of cancer cells, and can lead to complications such as kidney failure" This statement is incorrect: TLS does not cause a rapid breakdown of cancer cells; rather it is caused by a rapid breakdown of cancer cells. Please change to "The clinical experts explained that venetoclax plus rituximab is occasionally associated with tumour lysis syndrome, which is caused. This can cause by a rapid breakdown of cancer cells, and can lead to complications such as kidney failure"	Thank you for your comment**.** This has been amended in section 3.7 of the FAD.
35	Consultee	AbbVie	Pages 9 and 11 of the ACD refer to the model's time horizon as 20 years but this is factually inaccurate as the model time horizon is 30 years.	Thank you for your comment. This has been amended in section 3.10 of the FAD.
36	Commentators	Janssen	Janssen thank NICE for the opportunity to comment on the preliminary decision after the consideration of the evidence for venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia. We believe that all relevant evidence has been taken into account however, we would like to comment on Section 3.5 of the document.	Comment noted. No action required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Section 3.5 of the ACD discusses the committee's consideration of the MAIC presented by the manufacturer: *"The ERG also noted that patients had not been matched correctly, making the population in the RESONATE trial (ibrutinib) appear healthier than the population in the MURANO trial (venetoclax plus rituximab). This meant that the benefit of ibrutinib may have been underestimated."* Janssen believe the effectiveness of ibrutinib has been underestimated in the manufacturer's analysis. We agree that the incorrect matching along with other methodological choices cause the underestimation. The company did not adjust for important treatment effect modifiers such as number of prior therapies and percent of patients who are purine-analogue refractory. This is supported by the NICE DSU Technical Support Document 18. 1. National Institute of Health and Care Excellence. DSU Technical Support Document 18: Methods for Population-adjusted Indirect Comparisons in Submissions to NICE. Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf.	
37	Commentators	Clinical expert	Page 3: "1.1 Venetoclax with rituximab is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory chronic lymphocytic leukaemia in adults." *It is difficult to understand why such an important combination with over half of patients with relapsed CLL achieving MRD negative remissions with a fixed duration of therapy cannot be better than continuous therapy until resistance to therapy. The further follow-up of MURANO to 3 years indicates that stopping venetoclax therapy is safe.* "Relapsed or refractory chronic lymphocytic leukaemia is currently usually treated with ibrutinib. Clinical trial evidence suggests that venetoclax plus rituximab increases how long people live for before their disease gets worse compared with bendamustine plus rituximab (a combination that is	Comment noted. The committee discussed the benefits demonstrated by venetoclax plus rituximab including longer progression free survival and achieving negative minimal residual disease status. The committee concluded that venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab (See FAD section 3.4) and recommended venetoclax with rituximab for routine commissioning (See FAD section 3.17)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			rarely used now). Indirect comparisons of venetoclax plus rituximab with ibrutinib have limitations, so no firm conclusions can be drawn about the size of the benefit for venetoclax plus rituximab." *Both venetoclax (±rituximab) and ibrutinib are proven to be more effective than chemoimmunotherapy in relapsed CLL. The two drugs work in different and complementary ways and it is clear that patients crossing over from one drug to the other are likely to respond again. It does not seem logical to deny patients treatment with venetoclax plus rituximab because ibrutinib is effective. In fact it is important that both therapies are available for patients with the choice of sequencing being determined by patient choice or on cost pharmaco-economic criteria.* "For example, there are inconsistencies between the clinical- and cost-effectiveness data used because the costs of venetoclax treatment last for 2 years but the benefits continue for more than 2 years." *This is difficult to follow. How can stopping a therapy at 2 years with continued benefit beyond that point be a bad thing to happen. Maybe the pharmaco-economic model needs refining but it must be a good thing both for patients and economically!*	
38	Commentators	Gilead Sciences	Section 3.2 We request that the following statement is clarified and amended: *'This is because idelalisib plus rituximab has an intensive dosing regimen, and is associated with an increased risk of infection'* We do not agree that idelalisib plus rituximab should be regarded as a more intensive dosing regimen. Physicians familiar with the treatment of chronic lymphocytic leukaemia (CLL) and the use of idelalisib will be aware of the use of prophylactic medication to minimise the risk of treatment-related infections. The occurrence of treatment-related infections has also been described with the use of other treatments for relapsed or refractory CLL such as ibrutinib.	Comment noted. This has been included in section 3.2 of the FAD to reflect statement provided by the clinical expert.
39	Commentators	Gilead Sciences	We would like to draw the committee's attention to the growing body of evidence which postulates the potential benefit of using venetoclax as a later, rather than earlier line of therapy in CLL. For example, Deng et al. demonstrate that use of Bruton's tyrosine kinase inhibitors may increase BCL2 dependence of CLL cells, possibly enhancing the use of venetoclax when used as a later line of therapy, after treatments such as ibrutinib. Relevant references include: - Carter MJ et al. 2017. Leukemia 31, 1423-1433	Comment noted. In accordance with the Guide to the methods of technology appraisal 2013 section 6.1.12, for this topic the appraisal committee made recommendations regarding the use of venetoclax with rituximab within the terms of its UK marketing authorisation.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			(https://www.nature.com/articles/leu2016333) - Deng J et al. 2017. Leukemia. 2017 Oct;31(10):2075-2084 (https://www.ncbi.nlm.nih.gov/pubmed/28111464)	

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16th November 2018

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097] – Response to Appraisal Consultation Document (ACD)

Dear Helen,

Please provide a copy of this letter to Committee C. AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD). We wanted to emphasise at the outset that there are some factual inaccuracies in the ACD, which are presented in the NICE stakeholder comments template at the end of this letter. Additional evidence is presented in Appendix 1. We sincerely encourage the Committee to reconsider its draft guidance in light of this further information and clarification which is material to the conclusions within the ACD.

AbbVie is naturally disappointed that NICE has not at this stage recommended venetoclax in combination with rituximab (VEN+R) within its marketing authorisation for treating relapsed or refractory chronic lymphocytic leukaemia (R/R CLL). However, we are pleased that the committee acknowledged the benefits of a fixed treatment duration therapy to patients and concluded that VEN+R could be an important treatment option for people with R/R CLL. Furthermore, AbbVie welcomes the committee's conclusion that the economic model structure was appropriate for decision making. The request for additional analyses based on a recent data cut from the MURANO trial will also address some of the uncertainty in the modelling that was identified in the ACD.

AbbVie is pleased to confirm that with all patients off treatment and with a median of 3 years of follow-up, compelling efficacy results continue to be observed with VEN+R in addition to a safety profile that continues to be manageable, predictable and consistent with the known safety profile of both agents. The rate of CLL progression in the first 12 months after venetoclax completion was modest (13%), supporting the feasibility and safety of a time-limited duration of VEN+R. The median PFS in the VEN+R arm was not reached (55 events of progression or death in 194 patients; 28.4%). The median PFS in the BR arm was 17.0 months (144 events in 195 patients; 73.8%) (95% CI: 15.7, 21.7). There were no new safety signals. The prognostic significance of achieving undetectable MRD is well established: it leads to longer periods of remission and survival. A higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at completion of venetoclax treatment (i.e. month 24) in the VEN+R arm (48% uMRD) vs the BR arm (2% uMRD). Furthermore, VEN+R pts who achieved uMRD had durable PFS, thus providing biological plausibility for continued treatment benefit post the 2 year fixed treatment duration of VEN+R.

AbbVie welcomes the opportunity to address the committee's questions using the results of the recent data cut from the MURANO trial and has provided the following in response to the ACD (in appendix 1):

- Summary of efficacy data with all patients off treatment and with a median of 3 years follow-up, including progression free survival (PFS), overall survival (OS) and rate of clearance of MRD over time.

- Cost comparison between VEN+R and Ibrutinib. Page 12 of the ACD states: "*a cost comparison of venetoclax plus rituximab and ibrutinib is requested from the company, which might address these uncertainties*" i.e. assume equal efficacy (HRs=1). This is a conservative approach in the context of clinical expert comments in the ACD that VEN+R has similar or better efficacy to ibrutinib.
- Match adjusted indirect comparison (MAIC) results based on a recent data cut from the MURANO trial
- Scenario analyses accounting for loss of treatment effect after 2 years. Of note is that since the updated MAIC and survival analysis (using the recent data cut from the MURANO trial) already utilise data beyond the fixed treatment duration, adjusting treatment effect after 2 years is a pessimistic approach, as a loss of effect following treatment cessation would already be accounted for in the model.
- Scenarios where survival analysis for VEN+R uses the weighted population (as obtained from the MAIC) rather than the intention to treat (ITT) population (*i.e. extrapolation is based on the matched population rather than the original trial population*)
- Analysis including the utility values from the MURANO trial.

AbbVie notes the committee's comments in the ACD that cost-effectiveness estimates ranged widely from VEN+R being less costly and more effective to VEN+R being less costly and less effective when compared with ibrutinib. The updated analyses confirm that VEN+R is less costly and more effective than ibrutinib and the probability that VEN+R is cost-effective at a £20,000 per QALY threshold is 100% in both the list and net price comparisons. We acknowledge that the key driver of cost-effectiveness is the 2-year fixed treatment duration of VEN+R. Chemo-free fixed treatment duration is unprecedented in R/R CLL but is validated by a significant proportion of MURANO trial patients achieving undetectable minimal residual disease (MRD) status, which clinical experts agree is a strong predictor of lasting remission in patients with CLL as stated in the ACD. However fixed treatment duration is not unprecedented in CLL as combinations such as FCR have demonstrated long remissions[1]. Nevertheless, we remain open to a Cancer Drugs Fund (CDF) recommendation and anticipate that longer term follow-on data from the MURANO trial will reduce uncertainties in clinical and cost-effectiveness results. Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss further.

Yours sincerely,

[redacted]

[1] Kirsten Fischer et al (2016)"Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial." Blood 127, no. 2 (2016): 208-215.

NICE National Institute for Health and Care Excellence

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2018

email: TACommC@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name	AbbVie Ltd
Disclosure: Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	AbbVie is pleased to confirm that with all patients off treatment and with a median of 3 years of follow-up, compelling efficacy results continue to be observed with VEN+R in addition to a safety profile that continues to be manageable, predictable and consistent with the known safety profile of both agents. The rate of CLL progression in the first 12

	months after venetoclax completion was modest (13%), supporting the feasibility and safety of a time-limited duration of VEN+R. The median PFS in the VEN+R arm was not reached (55 events of progression or death in 194 patients; 28.4%). The median PFS in the BR arm was 17.0 months (144 events in 195 patients; 73.8%) (95% CI: 15.7, 21.7). There were no new safety signals. The prognostic significance of achieving undetectable MRD is well established: it leads to longer periods of remission and survival. A higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at completion of venetoclax treatment (i.e. month 24) in the VEN+R arm (48% uMRD) vs the BR arm (2% uMRD). Furthermore, VEN+R pts who achieved uMRD had durable PFS, thus providing biological plausibility for continued treatment benefit post the 2 year fixed treatment duration of VEN+R. AbbVie welcomes the opportunity to address the committee's questions using the results of the recent data cut from the MURANO trial and has provided additional analyses in Appendix 1. The main conclusion from these analyses is that VEN+R dominates ibrutinib and the probability that VEN+R is cost-effective compared with ibrutinib at £20,000 per QALY is 100% in both the list and net price comparisons. AbbVie acknowledges the uncertainties in the relative efficacy estimates based on the MAIC and has provided substantial evidence of a robust ICER (i.e. VEN+R dominates Ibrutinib) on which the committee can decide whether there is plausible potential for VEN+R to be cost-effective. Therefore VEN+R meets the criteria to be included in the CDF. AbbVie would welcome a CDF recommendation and anticipates that longer term follow-on data from the MURANO trial will reduce uncertainties in clinical and cost-effectiveness results.
2	Page 7 (3.5) states: "*The ERG also noted that patients had not been matched correctly, making the population in the RESONATE trial (ibrutinib) appear healthier than the population in the MURANO trial (venetoclax plus rituximab). This meant that the benefit of ibrutinib may have been underestimated*" This is factually inaccurate since the individual patient data came from the MURANO trial. The approach we took was to match the MURANO patient population to reflect the RESONATE patient population. Therefore, we made the MURANO population less healthy to match that of RESONATE, rather than the RESONATE population better off. Please also refer to page 47 of the ERG report
3	The ACD makes a number of statements suggesting that AbbVie's submission and economic model did not account for the 2 year fixed treatment duration of venetoclax in combination with rituximab – specifically not reflecting a change in treatment effect after 2 years. This is factually inaccurate and potentially misleading as Table 67, page 165 of the NICE submission includes a description of waning scenarios whereby the VEN+R treatment effect following treatment discontinuation is explored.
4	Page 3 states: "*There are problems with the economic model inputs. For example, there are inconsistencies between the clinical- and cost-effectiveness data used because the costs of venetoclax treatment last for 2 years but the benefits continue for more than 2 year*" The statement is potentially misleading. This is not an inconsistency – this is an assumption

	in the model based on clinical data and clinical expert opinion supporting ongoing treatment benefit beyond the 2 year fixed treatment duration. The prognostic significance of achieving uMRD is well established: it leads to longer periods of remission and survival. Supportive information was presented in the NICE submission: a higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at the end of combination therapy (EOCT) in the VEN+R arm vs BR arm (62% for VEN+R vs 13% for BR). The recent data cut confirms that this pattern was maintained at completion of treatment (i.e. at 24 months): 48% uMRD in the VEN+R arm vs 2% uMRD in the BR arm. Furthermore, VEN+R pts who achieved uMRD had durable PFS, thus providing biological plausibility for continued treatment benefit post the 2 year fixed treatment duration of VEN+R. Moreover, this is not unprecedented in CLL as fixed treatment duration combinations such as FCR have demonstrated long remissions. (Kirsten Fischer et al (2016)"Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial." Blood 127, no. 2 (2016): 208-215)
5	Pages 7 and 8, Section 3.5 states: "*The committee noted that the MAIC had not been adjusted to account for the fixed treatment duration of venetoclax, which may have resulted in a greater treatment benefit for venetoclax plus rituximab*". This is then used as justification for stating: "*The committee agreed that the MAIC was flawed*". This is factually inaccurate and potentially misleading. The fixed treatment duration of venetoclax is not a variable that can be adjusted for in population-adjusted indirect comparisons. Section 3.9, which repeats this factual inaccuracy should also be amended. Please also refer to comments 3 and 4 above.
6	Page 3, last paragraph and Page 11 (3.13) states: "*Estimates ranged widely from venetoclax plus rituximab being less costly and more effective to venetoclax plus rituximab being less costly and less effective when compared with ibrutinib* ***~~plus rituximab~~***" Please delete plus rituximab as the comparison is with ibrutinib monotherapy and not Ibrutinib with rituximab
7	Page 8 (3.17) states *"The clinical experts explained that venetoclax plus rituximab is occasionally associated with tumour lysis syndrome. This can cause a rapid breakdown of cancer cells, and can lead to complications such as kidney failure*" This statement is incorrect: TLS does not cause a rapid breakdown of cancer cells; rather it is caused by a rapid breakdown of cancer cells. Please change to "*The clinical experts explained that venetoclax plus rituximab is occasionally associated with tumour lysis syndrome,* ***which is caused~~. This can cause~~ by*** *a rapid breakdown of cancer cells, and can lead to complications such as kidney failure*"
8	Pages 9 and 11 of the ACD refer to the model's time horizon as 20 years but this is factually inaccurate as the model time horizon is 30 years.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of

comments from each organisation.

- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Appendix 1

Additional evidence provided in response to Appraisal Consultation Document (ACD)

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

November 2018

SUMMARY OF EFFICACY DATA WITH ALL PATIENTS OFF TREATMENT – MEDIAN FOLLOW-UP OF 3 YEARS USING MAY 2018 DATA CUT

(NB - efficacy analysis were based on investigator assessment only)

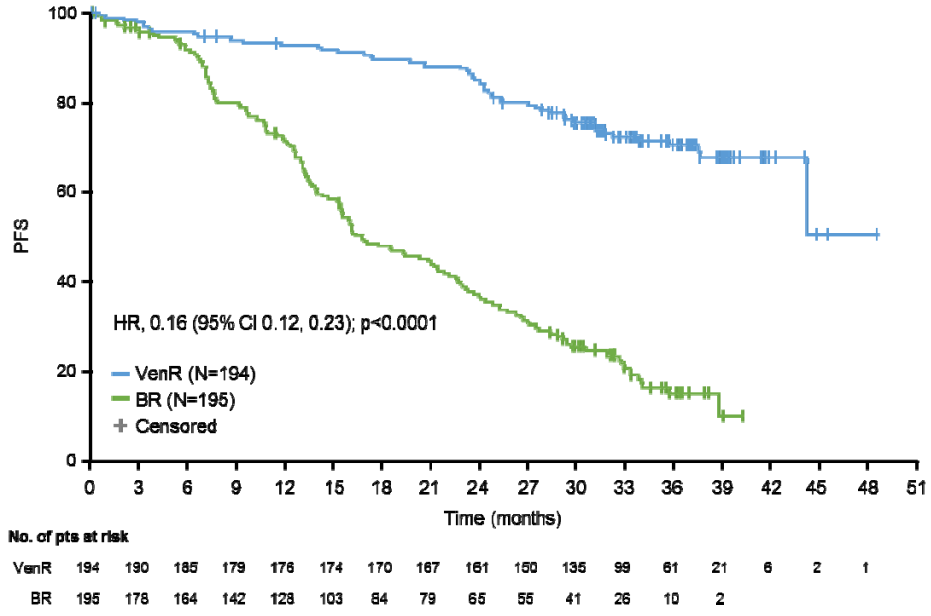
OVERVIEW

With all patients off treatment and with a median of 3 years of follow-up, compelling efficacy results continue to be observed with VEN+R in addition to a safety profile that continues to be manageable, predictable and consistent with the known safety profile of both agents. The rate of CLL progression in the first 12 months after venetoclax completion was modest (13%), supporting the feasibility and safety of a time-limited duration of VEN+R. The median PFS in the VEN+R arm was not reached (55 events of progression or death in 194 patients; 28.4%). The median PFS in the BR arm was 17.0 months (144 events in 195 patients; 73.8%) (95% CI: 15.7, 21.7). There were no new safety signals. The prognostic significance of achieving undetectable MRD is well established: it leads to longer periods of remission and survival. A higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at completion of venetoclax treatment (i.e. month 24) in the VEN+R arm (48% uMRD) vs the BR arm (2% uMRD). Furthermore, VEN+R pts who achieved uMRD had durable PFS, thus providing biological plausibility for continued treatment benefit post the 2 year fixed treatment duration of VEN+R.

1. Progression Free Survival

- The median PFS in the VEN+R arm was not reached (55 events of progression or death in 194 patients; 28.4%). The median PFS in the BR arm was 17.0 months (144 events in 195 patients; 73.8%) (95% CI: 15.7, 21.7).
- The risk of having a PFS event was reduced by 84% (stratified HR = 0.16; 95% CI: 0.12, 0.23; descriptive p value < 0.0001, stratified log-rank test) for patients in the VEN+R arm. The results of the unstratified analysis of PFS were similar to those for the stratified analysis.
- Progression-free estimates at 1, 2, and 3 years for the VEN+R versus (vs.) BR arm were 93% vs. 73%, 85% vs. 37%, and 71% vs. 15%, respectively.
- The K-M plot shows separation of the curves in favour of the VEN+R arm during the combination period which was maintained over time

Kaplan-Meier Plot of PFS (Investigator-Assessed) – Intent-to-Treat Patients

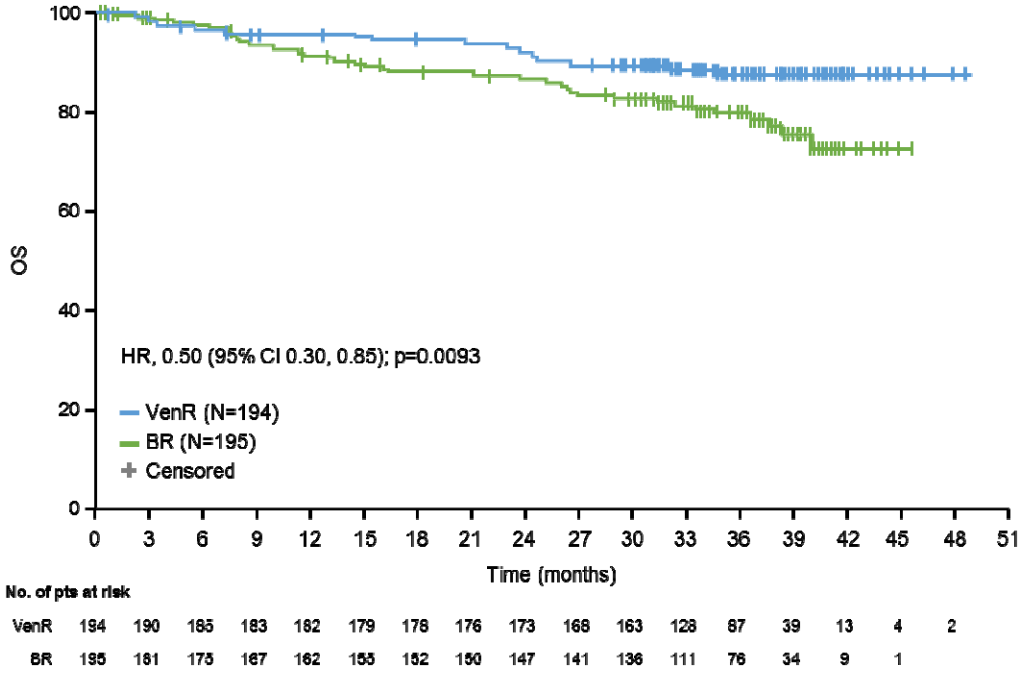


- Subgroup analyses of PFS as assessed by the investigator were performed to evaluate internal consistency of the primary efficacy analysis. As observed in the primary analysis, a consistent treatment benefit in favour of the VEN+R arm was observed in all high risk and low risk subgroups evaluated.

2. Overall Survival

- By the May 2018 data cut off, a total of 61 randomised patients had died; (22 [11.3%] patients in the VEN+R arm and 39 [20.0%] patients in the BR arm). Patients treated with the VEN+R combination continued to show a clinically meaningful improvement in overall survival over patients treated with BR.
- The K-M estimated median OS was not reached in either treatment arm. The estimated risk of death was decreased by 50% for patients treated with VEN+R compared to BR (stratified HR=0.50; 95% CI: 0.30, 0.85; descriptive p-value = 0.0093).
- The K-M plot shows separation of the curves in favour of the VEN+R arm, which was maintained over time

Kaplan-Meier Plot of OS – Intent-to-Treat Patients



3. Rate of clearance of MRD over time

- A higher peripheral blood (PB) undetectable MRD (uMRD) rate was observed at the end of combination therapy (EOCT) in the VEN+R arm vs BR arm (62% for VEN+R vs 13% for BR)
- The same pattern was observed at completion of venetoclax treatment (i.e. at month 24): 48% uMRD in the VEN+R arm vs 2% uMRD in the BR arm. Furthermore, consistently high uMRD rates were observed in all VEN+R subgroups, including patients with high-risk cytogenetics and molecular factors: del(17p) and/or *TP53* mutated: 57% at EOCT and 36% at month 24; *IGHV* unmutated: 61% at EOCT and 51% at month 24.
- VEN+R pts who achieved uMRD or intermediate MRD (int-MRD+) had durable PFS
- Please see the figure below - 130 pts in the VEN+R arm completed 2 yrs venetoclax treatment without disease progression; among them: 83 (64%) were uMRD, 23 (18%) were int-MRD+, 14 (10%) were high-MRD+ and 10

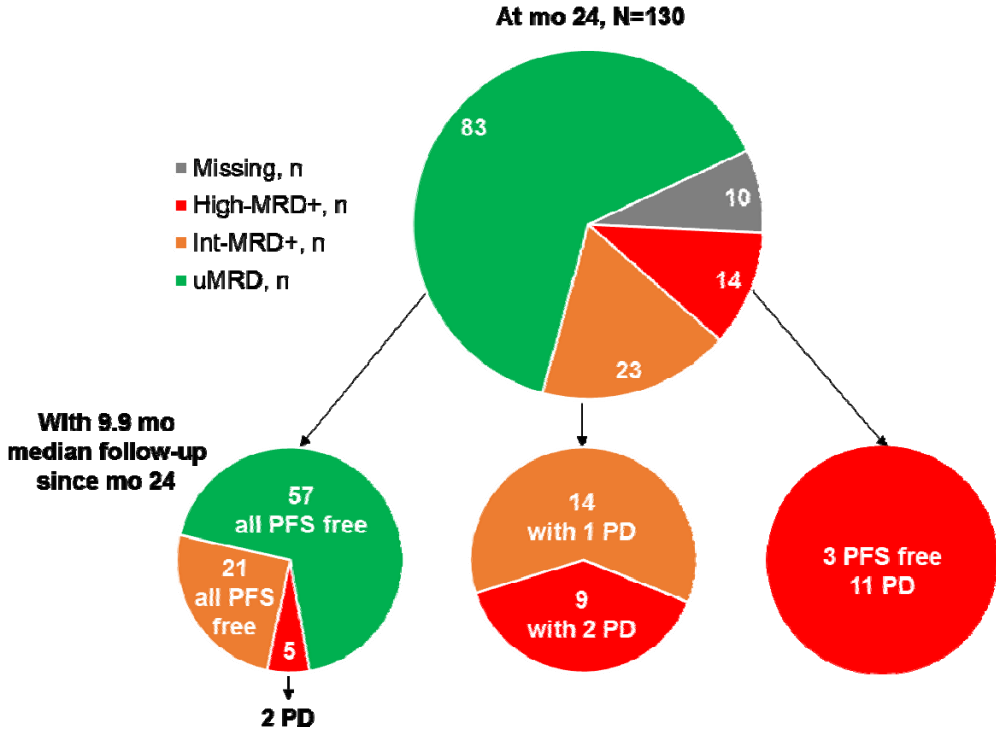
(8%) had missing data at month 24. With 9.9 month median follow-up from venetoclax completion, amongst uMRD pts at month 24, the majority remained uMRD (57/83, 69%) and 26/83 (31%) converted to confirmed MRD+ (2 serial assay positive). Conversions were mainly to int-MRD+ (21/26, 81%), all of whom remain PFS event-free; 19% (5/26) converted to high-MRD+, 2 had disease progression per iwCLL criteria

MRD status in pts at EOCT and end of therapy (24 months from Cycle 1 Day 1)

% of pts	VEN+R (N=194)		BR (N=195)	
	Mo 9 (EOCT)	Mo 24	Mo 9 (EOCT)	Mo 24
uMRD (<1 CLL cell per 10,000 leukocytes [$<10^{-4}$]),	62%	48%	13%	2%
Int-MRD+ ($\geq10^{-4}$ – $<10^{-2}$)	19%	16%	23%	7%
High-MRD+ ($\geq10^{-2}$)	5%	11%	29%	18%
Missing	7%	7%	15%	7%
disease progression/death/withdrew	7%	18%	20%	66%

B, bendamustine; C, cycle; D, day; EOCT, end of combination therapy; int, intermediate; mo, months; (u)MRD, (undetectable) minimal residual disease; pts, patients; R, rituximab; Ven, venetoclax

MRD changes in VEN+R arm pts who were progression-free at month 24 (n=130)



Int, intermediate; mo, month; (u)MRD, (undetectable) minimal residual disease; disease progression, disease progression; PFS, progression-free survival; pts, patients; VEN+R, venetoclax + rituximab

4. Safety

- There were no new safety signals.

ECONOMIC ANALYSES - MEDIAN OF 3 YEARS FOLLOW-UP

Executive Summary

The economic analyses present results of the recent data cut and explore scenarios requested by the committee:

1. Cost comparison of VEN+R vs Ibrutinib
2. Match adjusted indirect comparison (MAIC) results based on May 2018 data cut (methodology is the same as presented in the original NICE submission (document B and appendix)
3. Scenario analyses accounting for loss of treatment effect after 2 years
4. Scenario where VEN+R survival analyses uses the weighted population towards RESONATE rather than the ITT
5. Analysis including utility values from the MURANO trial

The conclusion from all these analyses is that VEN+R is less costly and more effective than ibrutinib.

The cost comparison of VEN+R vs ibrutinib assuming equal efficacy demonstrates that VEN+R is substantially lower in cost compared to ibrutinib.

The updated MAIC and cost-effectiveness analyses using the recent MURANO data cut demonstrates that VEN+R dominates ibrutinib and the probability that VEN+R is cost-effective at a £20,000 per QALY threshold is 100% in both the list and net price comparisons. VEN+R dominates Ibrutinib even when extremely pessimistic and clinically implausible scenarios showing loss of treatment effect after the 2 years fixed treatment duration of VEN+R are tested.

Although AbbVie believes that survival extrapolation should be based on the original trial population instead of the matched population in line with convention, the updated scenario analyses incorporating the committee's suggestion (i.e. extrapolation is based on the matched population) demonstrate that at both list price and net price, VEN+R dominates ibrutinib.

Finally, even when extreme differences between pre and post progression utilities are applied, VEN+R dominates ibrutinib in both list and net price comparisons.

AbbVie acknowledges the uncertainties in the relative efficacy estimates based on the MAIC and has provided substantial evidence of a robust ICER (i.e. VEN+R dominates Ibrutinib) on which the committee can decide whether there is plausible potential for VEN+R to be cost-effective. Therefore VEN+R meets the criteria to be included in the CDF. AbbVie would welcome a CDF recommendation and anticipates that longer term follow-on data from the MURANO trial will reduce uncertainties in clinical and cost-effectiveness results.

Cost comparison between VEN+R and ibrutinib

Section 3.13, page 12, of the ACD states "*The committee noted comments from the clinical experts that venetoclax plus rituximab has similar, or better, efficacy to ibrutinib (see section 3.5). It agreed that, because of uncertainties in the company's modelling, a cost comparison of venetoclax plus rituximab and ibrutinib is requested from the company, which might address these uncertainties*"

Based on the assumption that VEN+R and ibrutinib have equal efficacy (i.e. PFS and OS HRs of 1), a cost comparison is presented below. The table results below show that VEN+R ([redacted] at List price) is substantially lower in cost compared to ibrutinib ([redacted] at List price). Thus VEN+R is a cost-effective treatment option.

This simple analysis addresses some uncertainties in the cost-effectiveness estimates and AbbVie anticipates that longer term follow-on data from the MURANO trial will further reduce uncertainties in clinical and cost-effectiveness results. Therefore AbbVie remains open to a CDF recommendation.

Table 1 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 1 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with LIST prices)

[redacted]

Table 2 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 2 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

2. Match adjusted indirect comparison (MAIC) results based on May 2018 data cut

Section 3.13, page 11 of the ACD states "*It* [i.e. the committee] *concluded that some of the uncertainty in the modelling could be addressed by additional analyses based on a recent data cut from MURANO and by scenario analyses accounting for loss of treatment effect after 2 years*" This section presents the updated unanchored MAIC results using the May 2018 data cut from the MURANO trial, which was then used for the scenario analyses accounting for loss of treatment effect after 2 years. Please note that the methodology of the MAIC has been described in the NICE submission (document B); please refer to that document for a detailed description.

The analyses below (see section 2.1 and 2.2.1) show that with the recent data cut VEN+R dominates ibrutinib and the probability that VEN+R is cost-effective at £20,000 per QALY is 100% in both the list and net price comparisons.

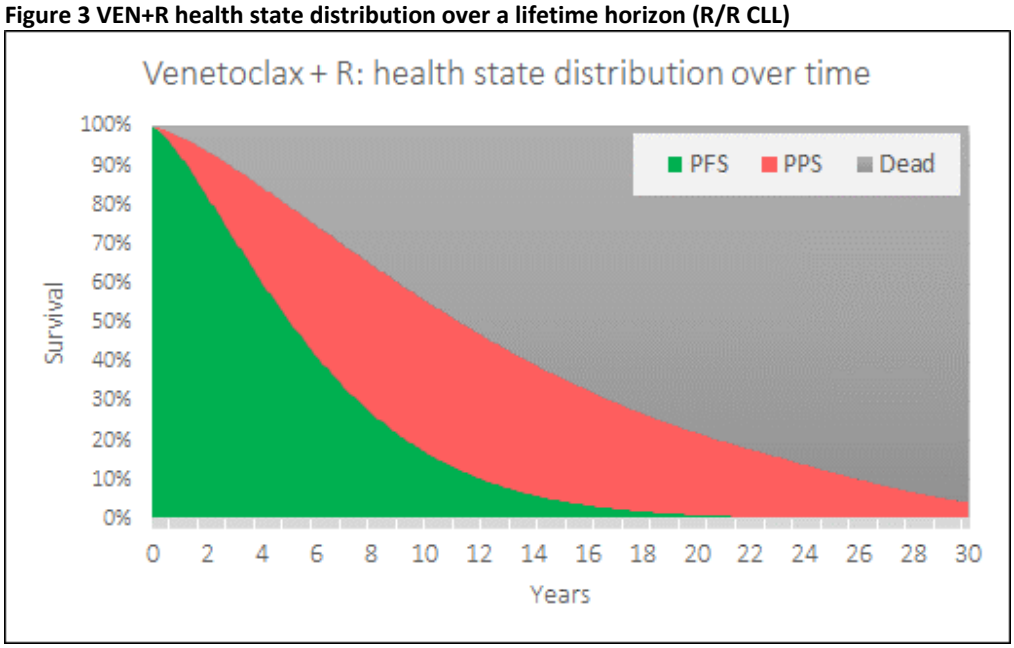
Table 3 MAIC comparisons (unanchored)

	Adjusted Comparison			Unadjusted Comparison		
	HR PFS (95% CI)	**HR OS (95% CI)**	**Sample Size**	**HR PFS (95% CI)**	**HR OS (95% CI)**	**Sample Size**
VEN+R vs. Ibrutinib	[redacted]	[redacted]	VEN+R=62 (Eff) Ibrutinib= 195	[redacted]	[redacted]	VEN+R= 169 Ibrutinib= 195

2.1 *Base-case results*

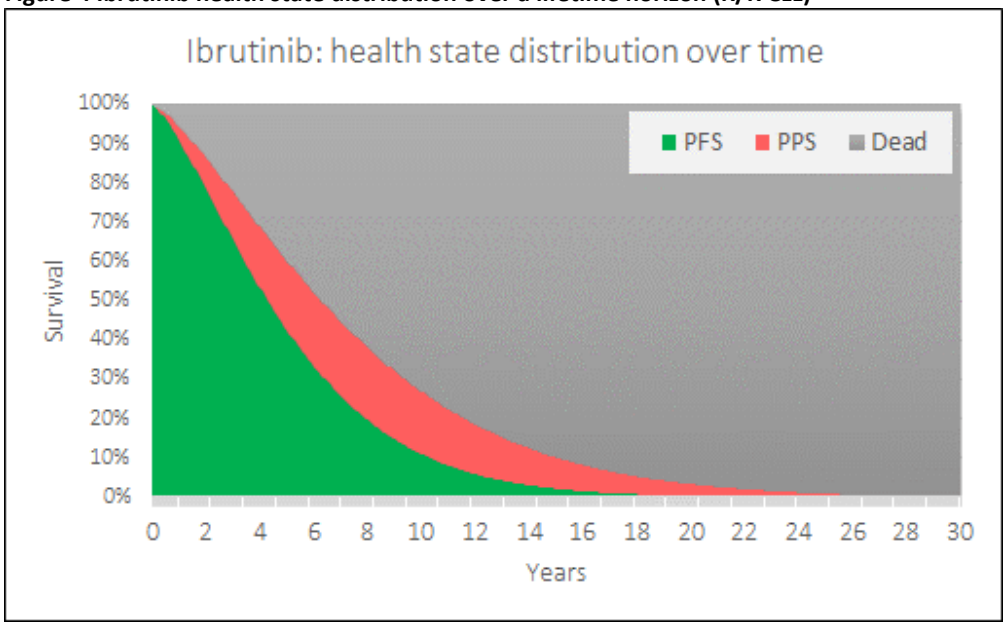
2.1.1 HEALTH STATE DISTRIBUTIONS OVER TIME

Figure 3 VEN+R health state distribution over a lifetime horizon (R/R CLL)



R, Rituximab; PFS, Progression Free Survival; PPS, Post-Progression Survival

Figure 4 Ibrutinib health state distribution over a lifetime horizon (R/R CLL)



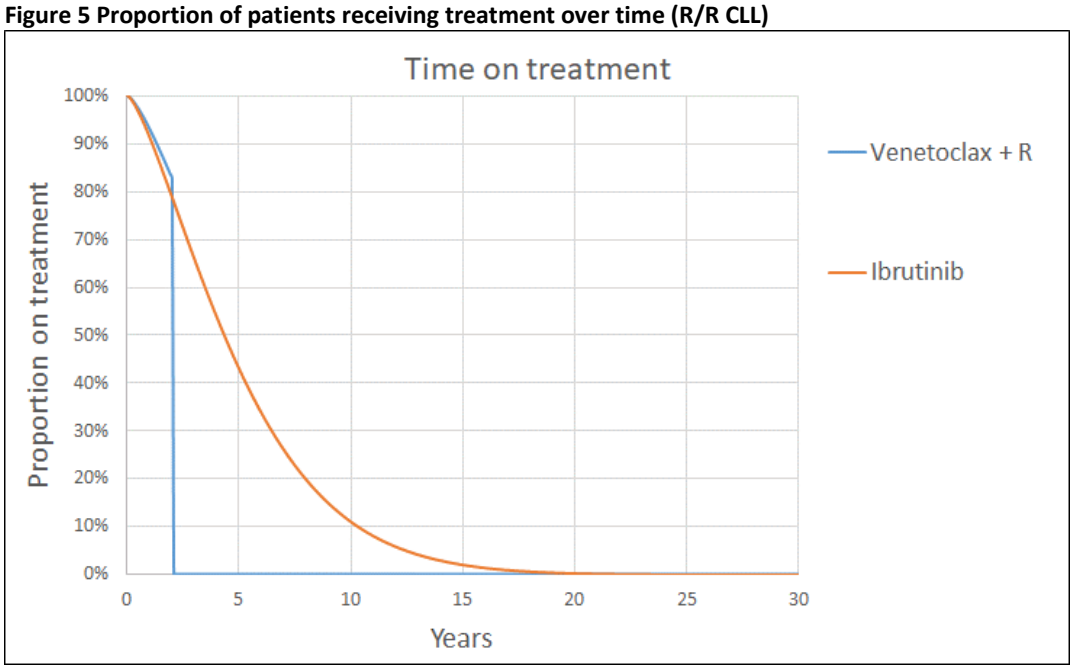
PFS, Progression Free Survival; PPS, Post-Progression Survival

2.1.2 TIME ON TREATMENT (TOT)

Table 4 Average time on treatment (R/R CLL)

Treatment	Average ToT (mean years)
Ibrutinib	5.181
VEN+R	1.914

Figure 5 Proportion of patients receiving treatment over time (R/R CLL)



2.1.3 COSTS

Table 5 Per patient costs by category, discounted over a lifetime horizon (R/R CLL)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event. [redacted]

2.1.4 QALYs

Table 6 Total per patient life years (undiscounted) and QALYs (discounted) over a lifetime horizon (R/R CLL)

	Undiscounted Life years			Discounted QALYs			
Treatment	**PFS**	**PPS**	**Total life years**	**Progression free QALYs**	**Post-progression QALYs**	**AE disutility**	**Total QALYs**
Ibrutinib	5.157	2.348	7.504	3.360	0.991	0.002	4.349
VEN+R	6.077	6.809	12.886	3.863	2.499	0.006	6.356

Key: PFS, Progression Free Survival; PPS, Post Progression Survival; AE, Adverse Event

2.1.5 INCREMENTAL COST-EFFECTIVENESS ANALYSIS RESULTS

The base case LIST and NET price results are presented below

Table 7 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
LIST Price							
Ibrutinib	[redacted]	7.50	4.349	-	-	-	-
VEN+R	[redacted]	12.89	6.356	[redacted]	5.382	2.007	VEN+R is Dominant
NET Price*							
Ibrutinib	[redacted]	7.50	4.349	-	-	-	-
VEN+ R	[redacted]	12.89	6.356	[redacted]	5.382	2.007	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio;LYG, life years gained; QALYs, quality-adjusted life years; * [redacted]

2.2 *Sensitivity analyses*

2.2.1 PROBABILISTIC SENSITIVITY ANALYSIS

Table 8 Base-case results (probabilistic, LIST price)

	Total costs (£), (95% CI)	Total QALYs, (95% CI)	Incremental. costs (£), (95% CI)	Incremental QALYs, (95% CI)	ICER (£/QALY), (95% CI)
Ibrutinib	[redacted]	4.332 (2.685, 6.070)	-	-	-
VEN+R	[redacted]	6.290 (4.703, 7.695)	[redacted]	1.958 (0.585, 3.344)	**VEN+R is dominant** [redacted]

Key:ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Figure 6 Incremental cost-effectiveness plane (R/R CLL, LIST price)

Key: QALY, quality adjusted life year;

Table 9 Base-case results (probabilistic, NET price)

	Total costs (£), (95% CI)	Total QALYs, (95% CI)	Incremental. costs (£), (95% CI)	Incremental QALYs, (95% CI)	ICER (£/QALY), (95% CI)
Ibrutinib	[redacted]	4.379 (2.677, 6.381)	-	-	-
VEN+R	[redacted]	6.334 (4.816, 7.727)	-£160,771 (-£241,747, -£92,434)	1.955 (0.676, 3.270)	**VEN+R is dominant** (-£288,722, -£32,783)

Key:; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Figure 7 Incremental cost-effectiveness plane (R/R CLL, NET price)

Key: QALY, quality adjusted life year;

Figure 8 Cost-effectiveness acceptability curves (R/R CLL, LIST price)

Key: QALY, quality adjusted life year, R, rituximab

Figure 9 Cost-effectiveness acceptability curves (R/R CLL, NET price)

Key: QALY, quality adjusted life year, R, rituximab

2.2.2 DETERMINISTIC SENSITIVITY ANALYSIS

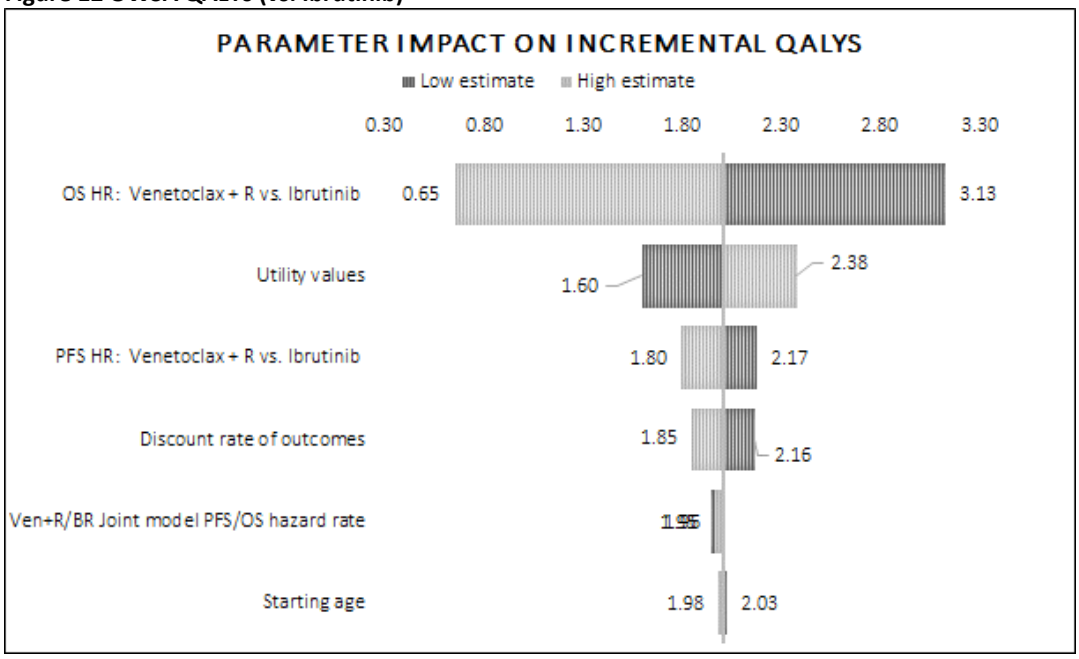
Figure 10 OWSA costs (vs. ibrutinib LIST price)

Key: HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome;

Figure 11 OWSA costs (vs. ibrutinib, NET price)

Key:; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome;

Figure 12 OWSA QALYs (vs. Ibrutinib)



Key:; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome;

Figure 13 OWSA NMB (vs. Ibrutinib, LIST price)

Key: HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome;

Figure 14 OWSA NMB (vs ibrutinib, NET price)

Key:; HR, hazard ratio; OS, overall survival; PFS, progression free survival; TLS, tumour lysis syndrome;

2.2.3 SCENARIO ANALYSIS

Table 10 Scenario analysis (R/R CLL, LIST price)

	VS. Ibrutinib		
	Inc. costs (£)	Inc. QALYs	ICER (£)
Base case	[redacted]	**2.007**	[redacted]
Discount rate. Costs: 0%, QALYs: 0%	[redacted]	3.085	[redacted]
Discount rate. Costs: 0%, QALYs: 6%	[redacted]	1.531	[redacted]
Discount rate. Costs: 6%, QALYs: 6%	[redacted]	1.531	[redacted]
Discount rate. Costs: 6%, QALYs: 0%	[redacted]	3.085	[redacted]
Time horizon: 5 year	[redacted]	0.275	[redacted]
Time horizon: 10 year	[redacted]	0.890	[redacted]
Time horizon: 15 year	[redacted]	1.429	[redacted]
Time horizon: 25 year	[redacted]	1.936	[redacted]
PFS/OS extrapolation: Generalised Gamma (Joint model)	[redacted]	1.956	[redacted]
PFS/OS extrapolation: Gamma (Joint model)	[redacted]	2.092	[redacted]
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Adjusted)	[redacted]	1.192	[redacted]
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Unadjusted)	[redacted]	1.488	[redacted]
Individual curve estimation for PFS and OS (adjusted)	[redacted]	0.752	[redacted]
Individual curve estimation for PFS and OS (naive)	[redacted]	1.952	[redacted]
TLS prophylaxis cost halved	[redacted]	2.007	[redacted]
TLS prophylaxis cost doubled	[redacted]	2.007	[redacted]
TLS prophylaxis cost removed	[redacted]	2.007	[redacted]
Pre and post-progression routine costs of care halved	[redacted]	2.007	[redacted]
Pre and post-progression routine costs of care doubled	[redacted]	2.007	[redacted]
Pre and post-progression routine costs of care removed	[redacted]	2.007	[redacted]
Pre and post-progression routine costs of care frequency from ibrutinib submission	[redacted]	2.007	[redacted]
Terminal care cost + 5%	[redacted]	2.007	[redacted]
Terminal care cost + 10%	[redacted]	2.007	[redacted]
Terminal care cost + 15%	[redacted]	2.007	[redacted]
Terminal care cost + 20%	[redacted]	2.007	[redacted]
All treatments use standard IV infusion of Rituximab	[redacted]	2.007	[redacted]
All treatments use rapid IV infusion of Rituximab	[redacted]	2.007	[redacted]
All treatments use subcutaneous injection of Rituximab	[redacted]	2.007	[redacted]
AE rates halved	[redacted]	2.009	[redacted]
AE rates doubled	[redacted]	2.003	[redacted]
AE removed	[redacted]	2.011	[redacted]
Utilities: Dretzke et al (PFS:0.800, PPS:0.600)	[redacted]	2.042	[redacted]
Utilities: Beusterien et al (PFS:0.819, PPS:0.680)	[redacted]	2.256	[redacted]
Disutilities doubled	[redacted]	2.003	[redacted]
Disutilities removed	[redacted]	2.011	[redacted]

Key: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Inc., incremental; IV, intravenous; OS, overall survival; PFS, progression free survival; PPS, post progression survival; QALY, quality adjusted life year; R, rituximab; TLS, tumour lysis syndrome; ToT, time on treatment;

Table 11 Scenario analysis (R/R CLL, NET price)

	VS. Ibrutinib		
	Inc. costs (£)	**Inc. QALYs**	**ICER (£)**
Base case	**-160,506**	**2.007**	**VEN+R is Dominant**
Discount rate. Costs: 0%, QALYs: 0%	-182,554	3.085	VEN+R is Dominant
Discount rate. Costs: 0%, QALYs: 6%	-182,554	1.531	VEN+R is Dominant
Discount rate. Costs: 6%, QALYs: 6%	-146,381	1.531	VEN+R is Dominant
Discount rate. Costs: 6%, QALYs: 0%	-146,381	3.085	VEN+R is Dominant
Time horizon: 5 year	-109,871	0.275	VEN+R is Dominant
Time horizon: 10 year	-159,673	0.890	VEN+R is Dominant
Time horizon: 15 year	-165,420	1.429	VEN+R is Dominant
Time horizon: 25 year	-161,476	1.936	VEN+R is Dominant
PFS/OS extrapolation: Generalised Gamma (Joint model)	-149,885	1.956	VEN+R is Dominant
PFS/OS extrapolation: Gamma (Joint model)	-176,281	2.092	VEN+R is Dominant
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Adjusted)	-231,931	1.192	VEN+R is Dominant
Assumption IBRUTINIB efficacy = IBRUTINIB +BR (Unadjusted)	-188,026	1.488	VEN+R is Dominant
Individual curve estimation for PFS and OS (adjusted)	-218,609	0.752	VEN+R is Dominant
Individual curve estimation for PFS and OS (naive)	-161,236	1.952	VEN+R is Dominant
TLS prophylaxis cost halved	-161,492	2.007	VEN+R is Dominant
TLS prophylaxis cost doubled	-158,532	2.007	VEN+R is Dominant
TLS prophylaxis cost removed	-162,479	2.007	VEN+R is Dominant
Pre and post-progression routine costs of care halved	-168,285	2.007	VEN+R is Dominant
Pre and post-progression routine costs of care doubled	-144,946	2.007	VEN+R is Dominant
Pre and post-progression routine costs of care removed	-176,065	2.007	VEN+R is Dominant
Pre and post-progression routine costs of care frequency from ibrutinib submission	-169,477	2.007	VEN+R is Dominant
Terminal care cost + 5%	-160,549	2.007	VEN+R is Dominant
Terminal care cost + 10%	-160,593	2.007	VEN+R is Dominant
Terminal care cost + 15%	-160,637	2.007	VEN+R is Dominant
Terminal care cost + 20%	-160,611	2.007	VEN+R is Dominant
All treatments use standard IV infusion of Rituximab	-160,244	2.007	VEN+R is Dominant
All treatments use rapid IV infusion of Rituximab	-160,618	2.007	VEN+R is Dominant
All treatments use subcutaneous injection of Rituximab	-161,451	2.007	VEN+R is Dominant
AE rates halved	-160,678	2.009	VEN+R is Dominant
AE rates doubled	-160,161	2.003	VEN+R is Dominant
AE removed	-160,850	2.011	VEN+R is Dominant
Utilities: Dretzke et al (PFS:0.800, PPS:0.600)	-160,506	2.042	VEN+R is Dominant
Utilities: Beusterien et al (PFS:0.819, PPS:0.680)	-160,506	2.256	VEN+R is Dominant
Disutilities doubled	-160,506	2.003	VEN+R is Dominant
Disutilities removed	-160,506	2.011	VEN+R is Dominant

Key: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; Inc., incremental; IV, intravenous; OS, overall survival; PFS, progression free survival; PPS, post progression survival; QALY, quality adjusted life year; R, rituximab; TLS, tumour lysis syndrome; ToT, time on treatment;

3. Scenario analyses accounting for loss of treatment effect after 2 years

The VEN+R treatment effect following treatment discontinuation can be explored by manipulating the VEN+R hazards. This is done by incorporation of a waning effect assumed to start after 2 years, i.e. immediately after treatment cessation. More specifically, hazards (loss of treatment effect) increase by a user specified amount per year immediately after two years. The hazard multiplier continues until the final model cycle. The results of annual 5%, 10%, 20%, 30% and 40%, increases in hazard are presented. Hazard functions are presented alongside survival curves and show the growing distance between the original and waning effect hazard ratio. There are two important points to note:

a) Adjusting treatment effect after 2 years is a pessimistic approach, since the updated MAIC and survival analysis (using the 3-year follow-up data cut) already utilises data beyond the 2 year fixed treatment duration: in other words, a loss of effect following treatment cessation would already be accounted for in the model.
b) Page 71, table 16 of the ERG report summarises the range of extrapolated VEN+R OS outcomes considered reasonable by clinical expert opinion. The VEN+R 20-year OS outcome used in AbbVie's base case model is [redacted] (based on Weibull), which falls within the conservative end of the range of outcomes considered reasonable by clinical expert opinion. However the ERG considered AbbVie's model selection too pessimistic and selected the gamma model which predicted VEN+R 20-year OS as [redacted]. Figure 15 below shows that a waning (loss of treatment effect) of 5% per year, which predicts roughly ten percent of patients alive at 20 years is at the conservative end of the range of outcomes considered plausible by clinical experts. However, a waning of 10% per year is too pessimistic as the percentage of patients alive at 20 years in this scenario is 0%, which is not clinically plausible as per clinical expert opinion. AbbVie has gone further in presenting results for 20%, 30% and 40%, which are even less clinically plausible.

In conclusion VEN+R dominates Ibrutinib even when extreme waning scenarios accounting for loss of treatment effect after 2 years are applied.

Figure 15 VEN+R PFS and OS waning effect (5% per year after FTD)

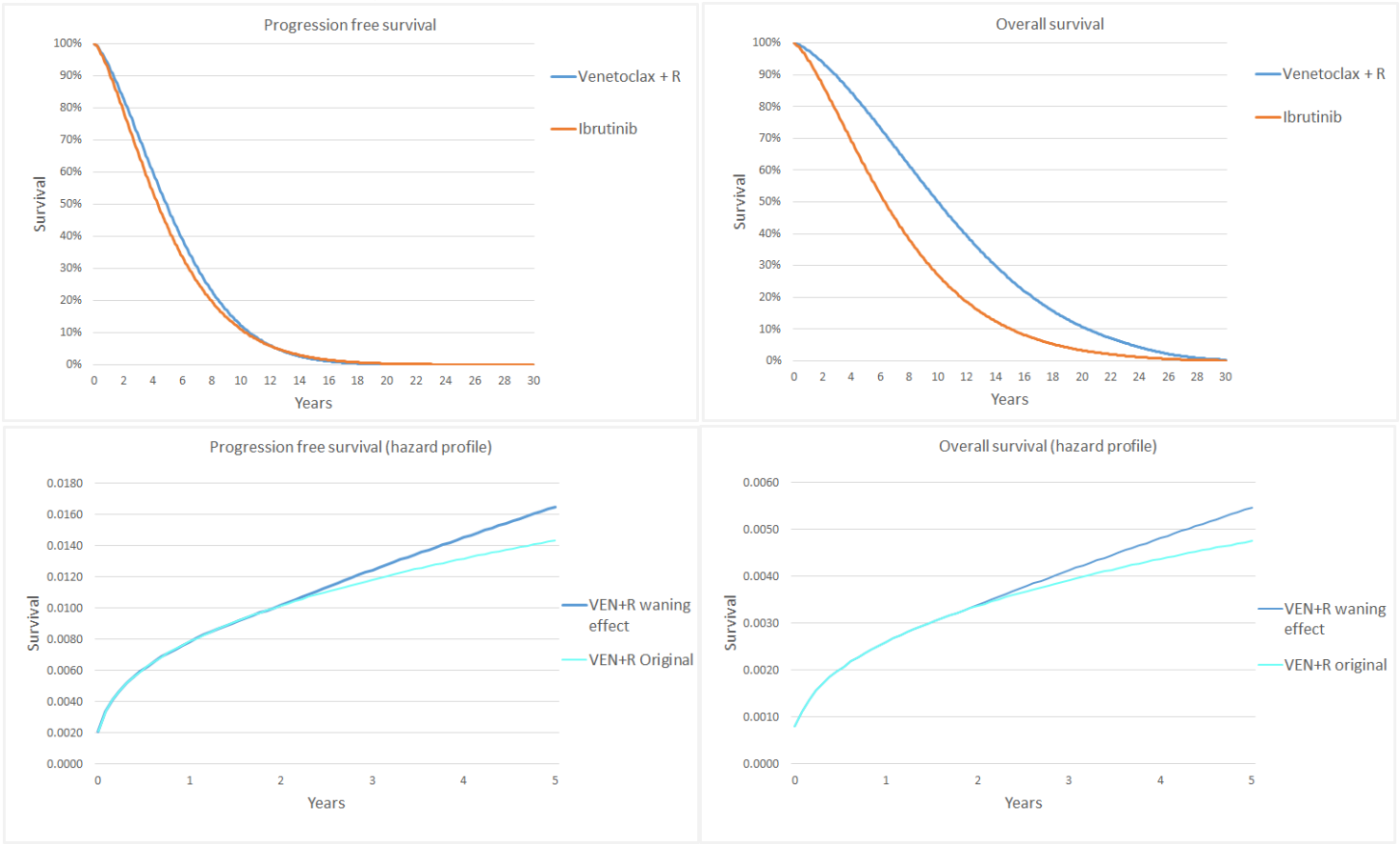


Table 12 VEN+R waning effect (5% per year after FTD)

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LIST price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R	[redacted]	5.736	[redacted]	1.387	VEN+R is Dominant
NET price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R	[redacted]	5.736	-£164,238	1.387	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Figure 16 VEN+R PFS and OS waning effect (10% per year after FTD)

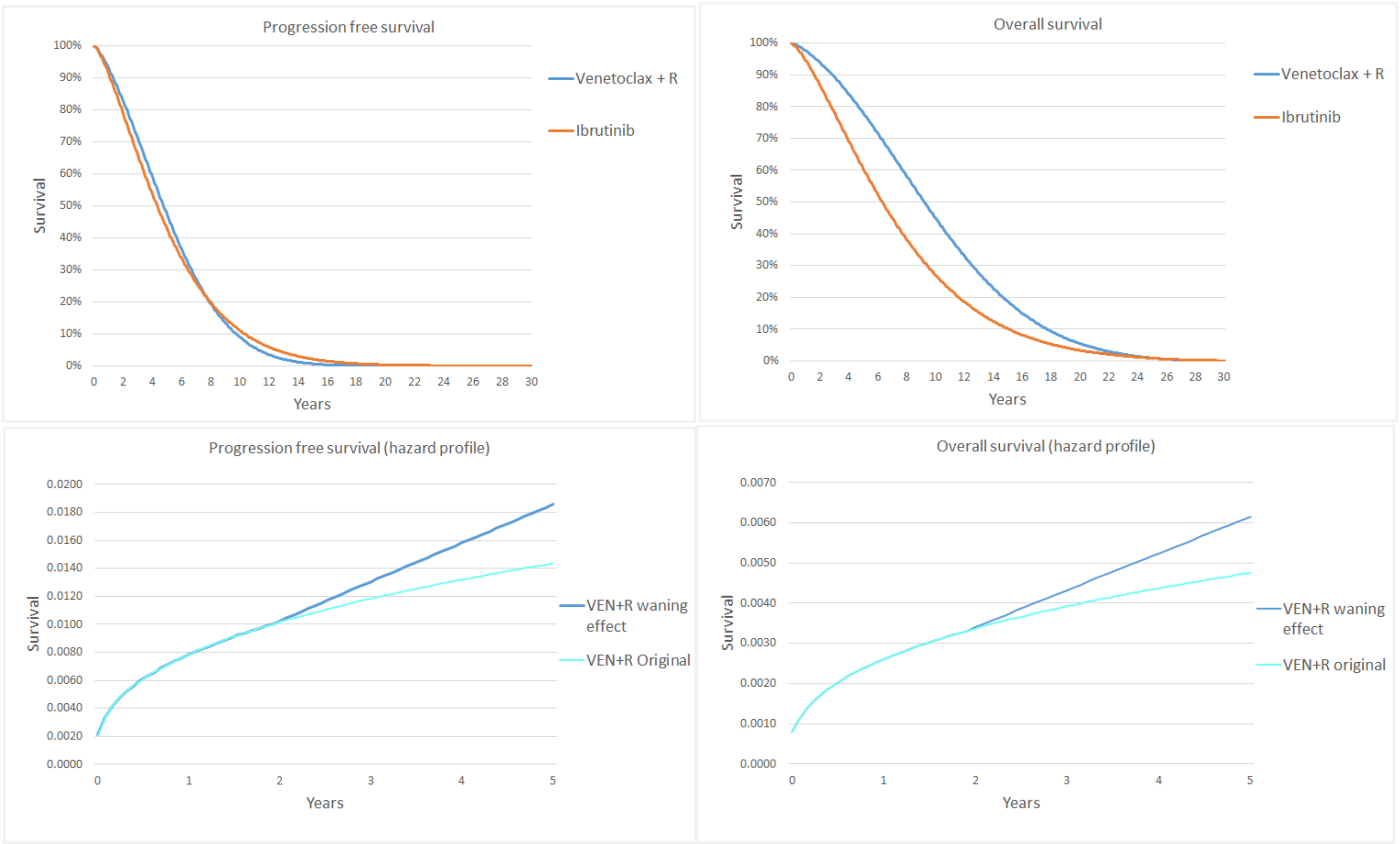


Table 13 VEN+R waning effect (10% per year after FTD)

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LIST price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R	[redacted]	5.367	[redacted]	1.018	VEN+R is Dominant
NET price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R	[redacted]	5.367	-£166,369	1.018	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Figure 17 VEN+R PFS and OS waning effect (20% per year after FTD)

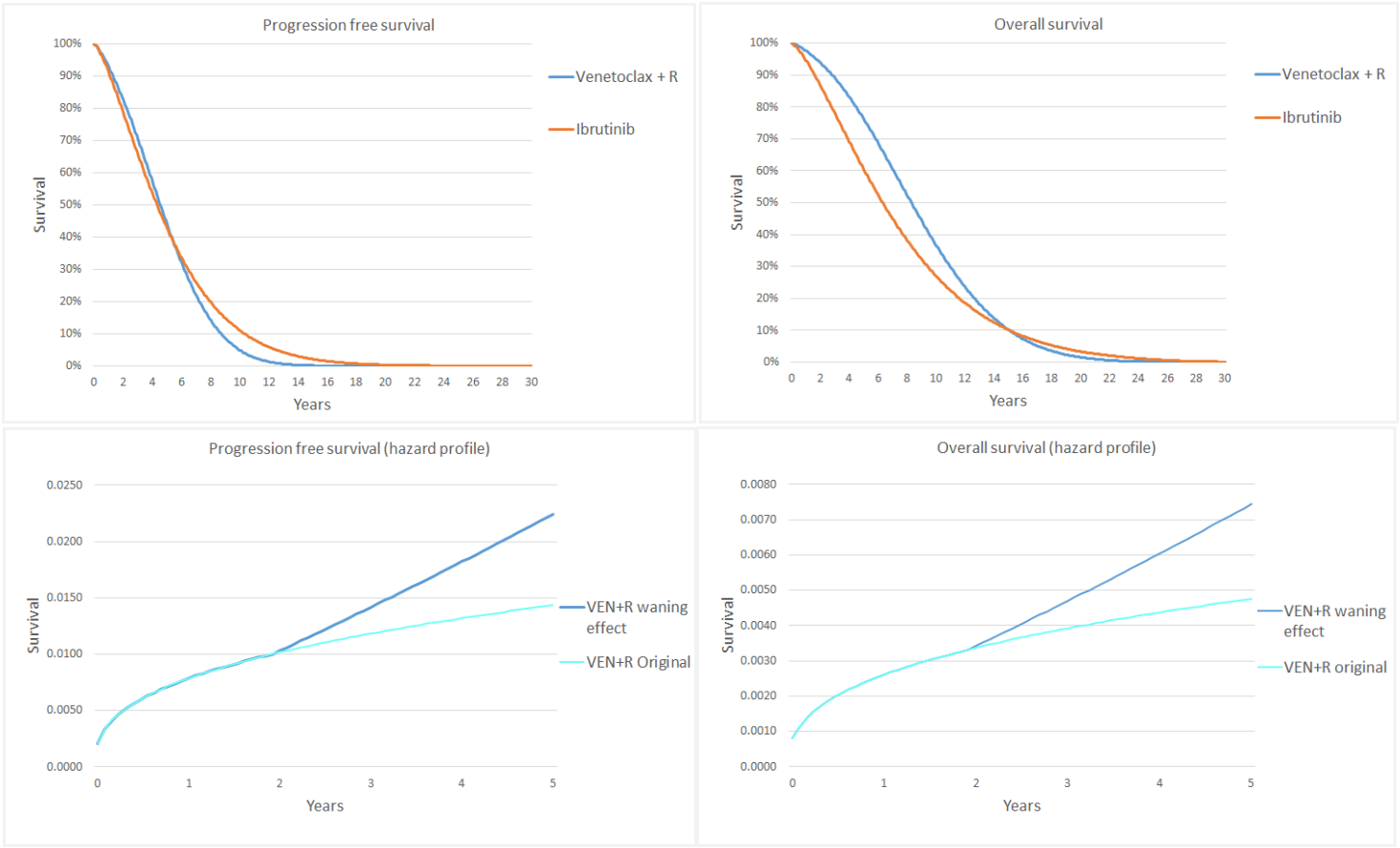


Table 14 VEN+R waning effect (20% per year after FTD)

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LIST price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+R	[redacted]	4.918	[redacted]	0.570	VEN+R is Dominant
NET price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+R	[redacted]	4.918	-£168,810	0.570	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Figure 18 VEN+R PFS and OS waning effect (30% per year after FTD)

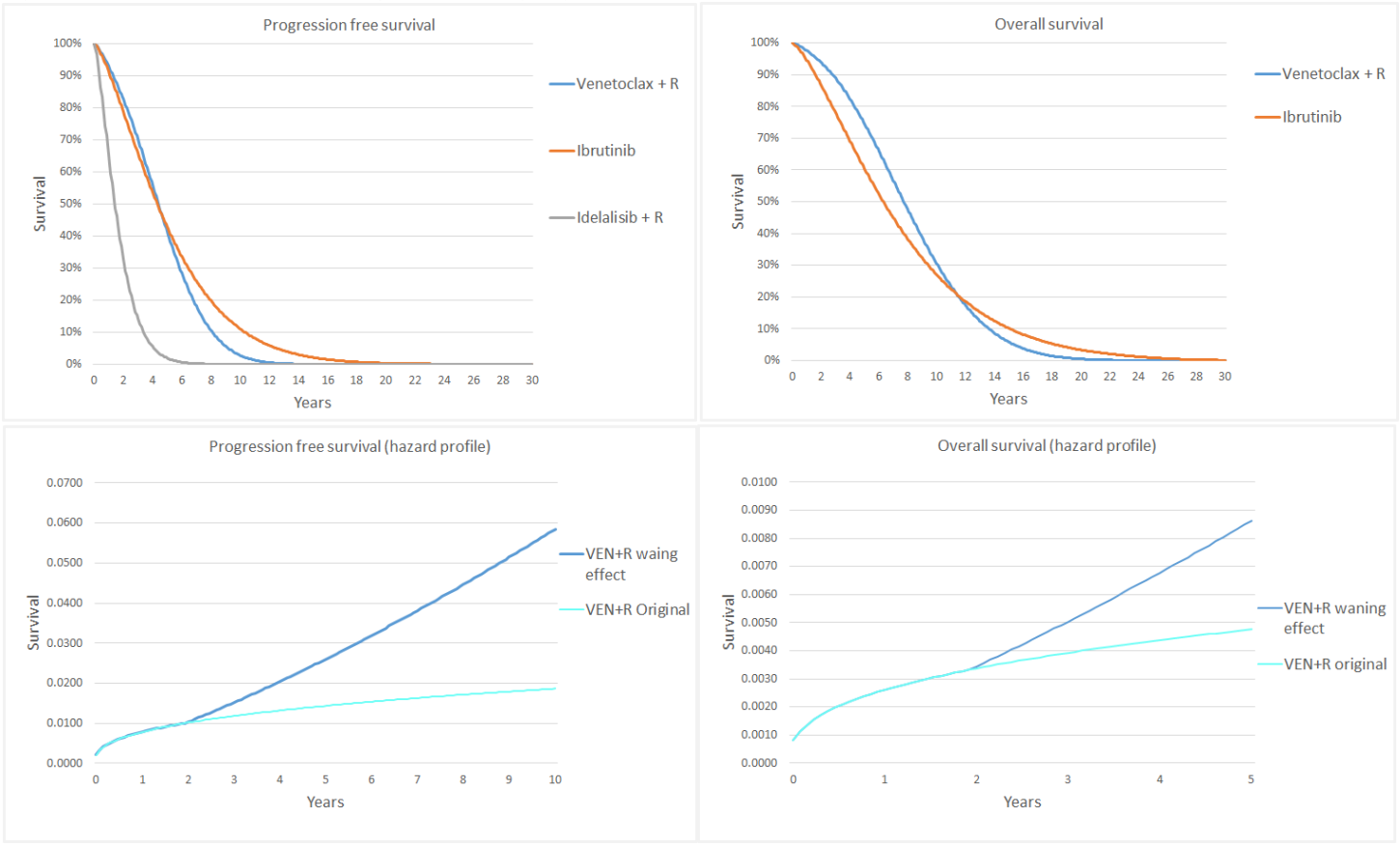


Table 15 VEN+R waning effect (30% per year after FTD)

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LIST price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+R	[redacted]	4.640	[redacted]	0.291	VEN+R is Dominant
NET price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+R	[redacted]	4.640	-£170,241	0.291	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Figure 19 VEN+R PFS and OS waning effect (40% per year after FTD)

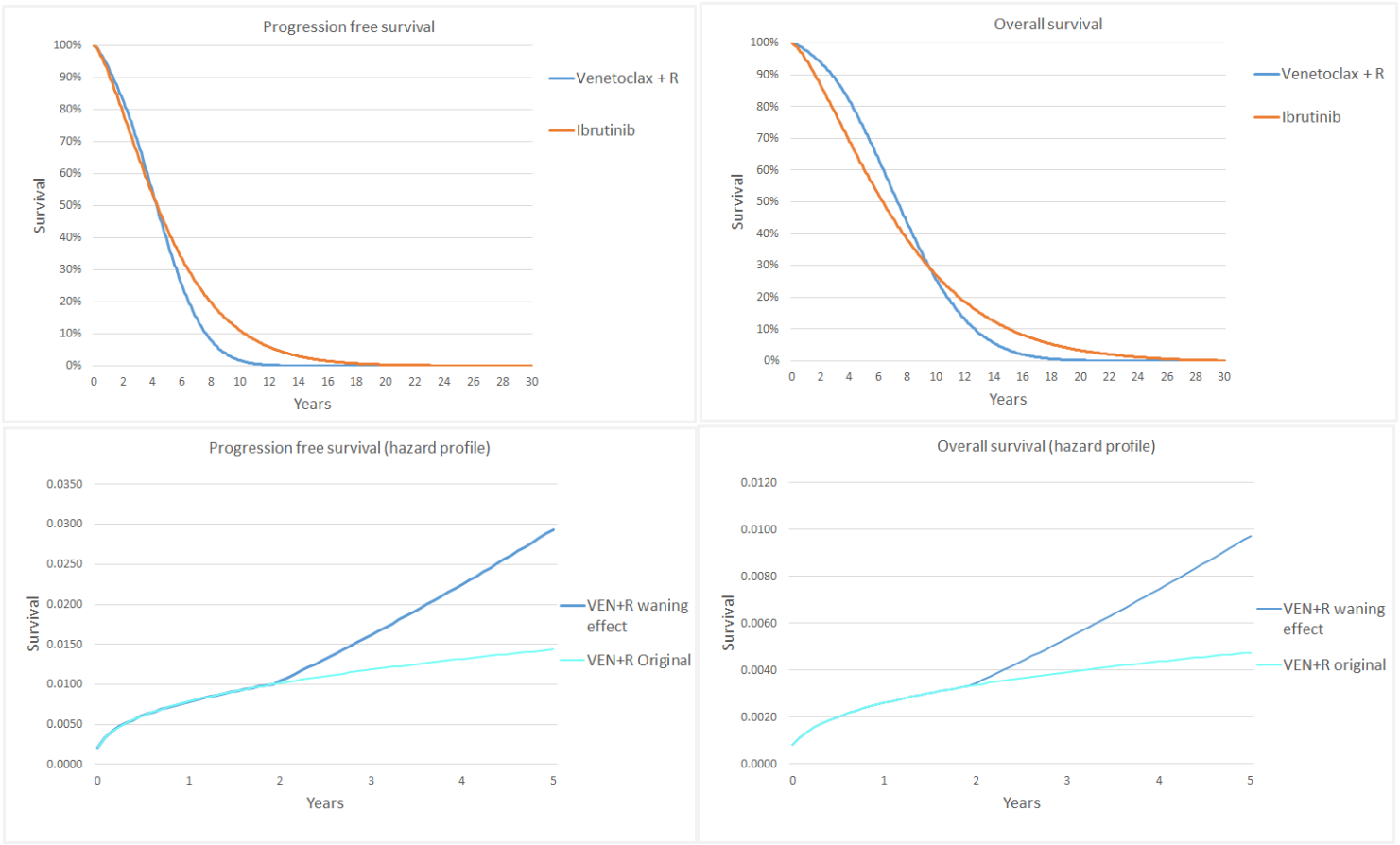


Table 16 VEN+R waning effect (40% per year after FTD)

	Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LIST price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+R	[redacted]	4.444	[redacted]	0.095	VEN+R is Dominant
NET price	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+R	[redacted]	4.444	-£171,216	0.095	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

4. Scenario where VEN+R survival analyses uses the weighted population towards RESONATE rather than the ITT

Section 3.9, page 9 of the ACD states: "*The committee noted that, because the extrapolation was based on the original trial population instead of the matched population, the extrapolation did not represent the correct population*" AbbVie believes the conventional approach is to use the original trial population (i.e. ITT). Nevertheless, this section presents the results of a scenario in which the extrapolation is based on the matched population. The analysis shows that at both list price and net price, VEN+R dominates ibrutinib.

A fair comparison between the RESONATE (ibrutinib) and MURANO (VEN+R) studies requires minimising biases in the baseline characteristics. In the MAIC, propensity score weighting was used to ensure effect modifying characteristics at baseline are comparable. This was done to estimate adjusted hazard ratios (for VEN+R vs IBRU, PFS and OS), which were applied to the MURANO baseline survival curves. Instead of using the ITT MURANO curves, this analysis fits extrapolations to the RESONATE-weighted population of MURANO instead. In effect, this is an estimate of what VEN+R and BR's extrapolations might look like if they had been administered in the RESONATE population (based on observed characteristic adjustments).

After including patient weights, the parametric extrapolations were carried out on 169 VEN+R patients and 159 BR patients. The joint model estimated below assumes the model specification for the base-case as described in the original NICE submission – document B (i.e. proportionally between treatments and endpoints). Table 19 presents the key estimated survival outcomes and model fit parameters (AIC and BIC) for the joint model. Figure 200 presents the graphical output of the model fit and extrapolated outcomes stratified by endpoint. As the lowest AIC and BIC numbers are considered to indicate the better fitting models, the Gompertz distribution provides the best fitting model for the weighted MURANO population. The Weibull distribution provides the second best fitting model based on the AIC and BIC values. The Gompertz distribution has been excluded in the subsequent analyses on the basis of implausibly short survival outcomes despite fitting the observed data well. Furthermore the Weibull parameterisation has been maintained for the base-case PFS and OS curves (Figures 21 and 22) and results (Table 17) in order to maintain consistency with the MURANO ITT models initially submitted to NICE. Table 18 presents a scenario analysis with alternatives parametric distributions and in all scenarios VEN+R dominates ibrutinib

Table 17 VEN+R weighted towards RESONATE (Weibull model with LIST and NET prices)

		Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
LIST price	Ibrutinib	[redacted]	4.417	-	-	-
	VEN+R	[redacted]	6.407	[redacted]	-1.990	VEN+R is Dominant
NET price	Ibrutinib	[redacted]	4.417	-	-	-
	VEN+R	[redacted]	6.407	-£136,976	-1.990	VEN+R is Dominant

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years;

Table 18 Scenario analysis with parametric distributions (with LIST and NET prices)

	VS. Ibrutinib (list prices)			VS. Ibrutinib (net prices)		
PFS/OS extrapolation	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£)**
Base case (Weibull)	[redacted]	**1.990**	**VEN+R is Dominant**	**-136,976**	**1.990**	**VEN+R is Dominant**
Generalised Gamma	[redacted]	1.951	VEN+R is Dominant	-128,127	1.951	VEN+R is Dominant
Gamma	[redacted]	2.086	VEN+R is Dominant	-153,613	2.086	VEN+R is Dominant
Log-logistic	[redacted]	2.095	VEN+R is Dominant	-174,864	2.095	VEN+R is Dominant
Log-normal	[redacted]	2.265	VEN+R is Dominant	-221,983	2.265	VEN+R is Dominant

Table 19- AIC, BIC and survival outcomes from estimated parametric modelling of VEN+R and BR PFS and OS for patients in the MURANO trial weighted by effect modifying characteristics from the RESONATE trial

Outcomes			Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gamma	Gen gamma
AIC			1986.09	1971.58	1961.42	1981.18	2006.83	1975.22	1971.95
BIC			2030.95	2020.93	2010.77	2030.53	2056.18	2024.56	2025.79
BR PFS	Median (years)		1.28	1.42	1.55	1.38	1.39	1.37	1.48
	Survival %	2-year	34.0%	32.6%	35.7%	34.7%	38.6%	32.7%	33.5%
		5-year	6.7%	1.7%	0.0%	9.9%	15.2%	3.4%	0.7%
		10-year	0.5%	0.0%	0.0%	3.2%	5.6%	0.1%	0.0%
		20-year	0.0%	0.0%	0.0%	1.0%	1.6%	0.0%	0.0%
BR OS	Median (years)		6.28	4.95	4.10	4.64	4.66	4.99	5.08
	Survival %	2-year	80.2%	82.5%	85.2%	81.0%	75.2%	81.4%	82.9%
		5-year	57.6%	49.6%	30.4%	46.8%	47.8%	49.9%	50.8%
		10-year	33.2%	15.4%	0.0%	21.1%	27.0%	19.1%	13.8%
		20-year	11.0%	0.7%	0.0%	7.5%	12.0%	2.3%	0.1%
VEN+R PFS	Median (years)		5.53	4.57	3.86	4.69	5.49	4.76	4.51
	Survival %	2-year	77.8%	80.6%	83.0%	81.3%	79.2%	80.3%	80.3%
		5-year	53.5%	45.6%	25.0%	47.3%	53.0%	47.8%	44.6%
		10-year	28.6%	12.3%	0.0%	21.4%	31.5%	17.4%	9.0%
		20-year	8.2%	0.4%	0.0%	7.6%	14.9%	1.9%	0.0%
VEN+R OS	Median (years)		20.05	11.72	6.19	11.63	13.45	12.55	11.89
	Survival %	2-year	93.3%	94.5%	95.5%	95.4%	93.8%	94.5%	94.1%
		5-year	84.1%	81.2%	70.8%	81.0%	78.7%	81.6%	81.5%
		10-year	70.8%	57.5%	0.3%	56.5%	59.5%	59.7%	58.4%
		20-year	50.1%	22.9%	0.0%	28.3%	37.5%	28.7%	21.5%

Figure 20- Parametric models for joint estimation of OS and PFS for VEN+R and BR for patients in the MURANO trial weighted by effect modifying characteristics from the RESONATE trial

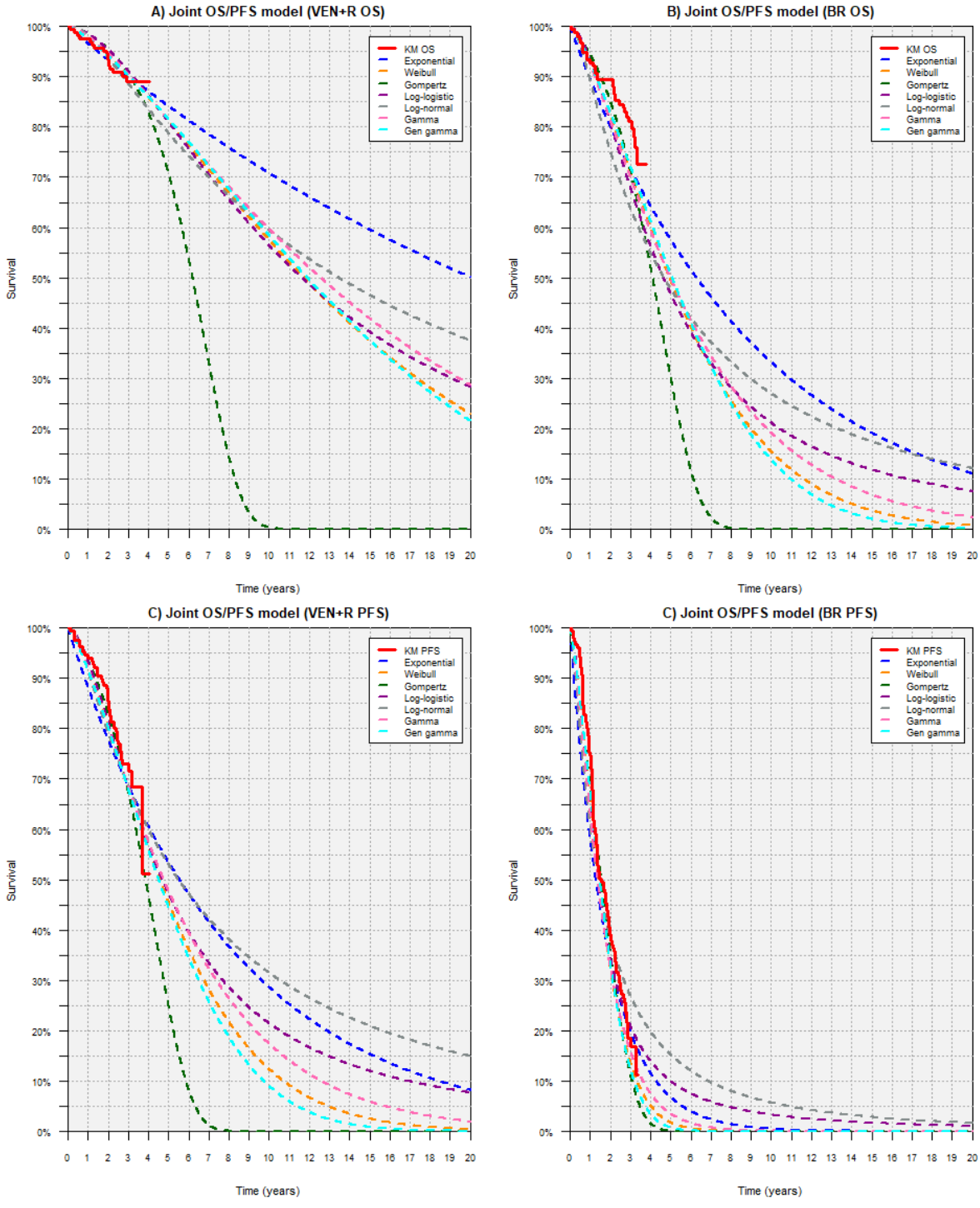


Figure 21 PFS curves (VEN+R weighted towards RESONATE, Weibull model)

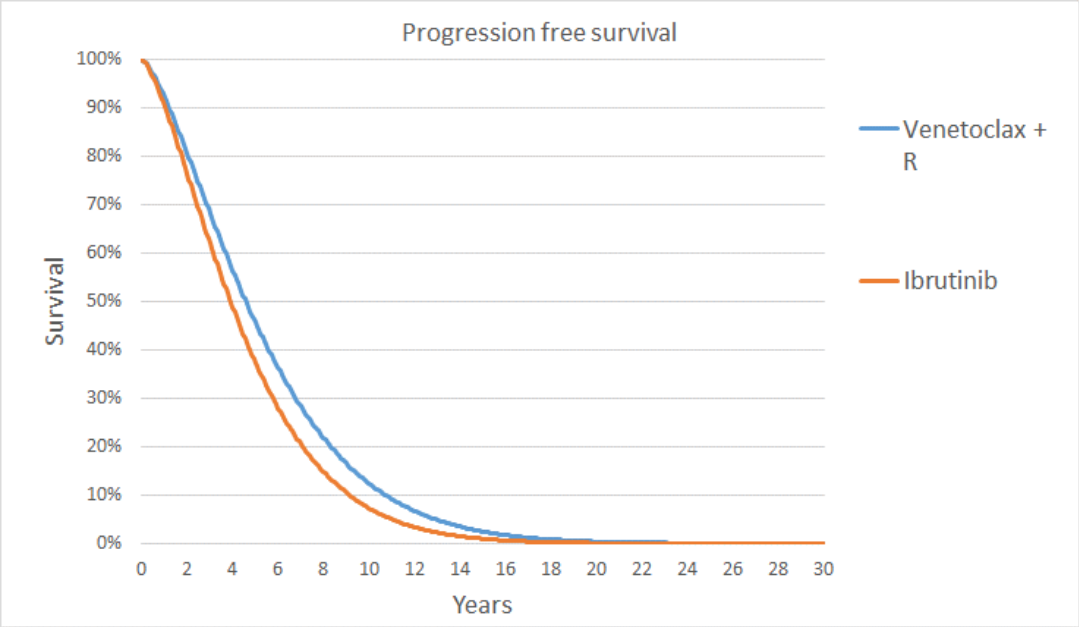
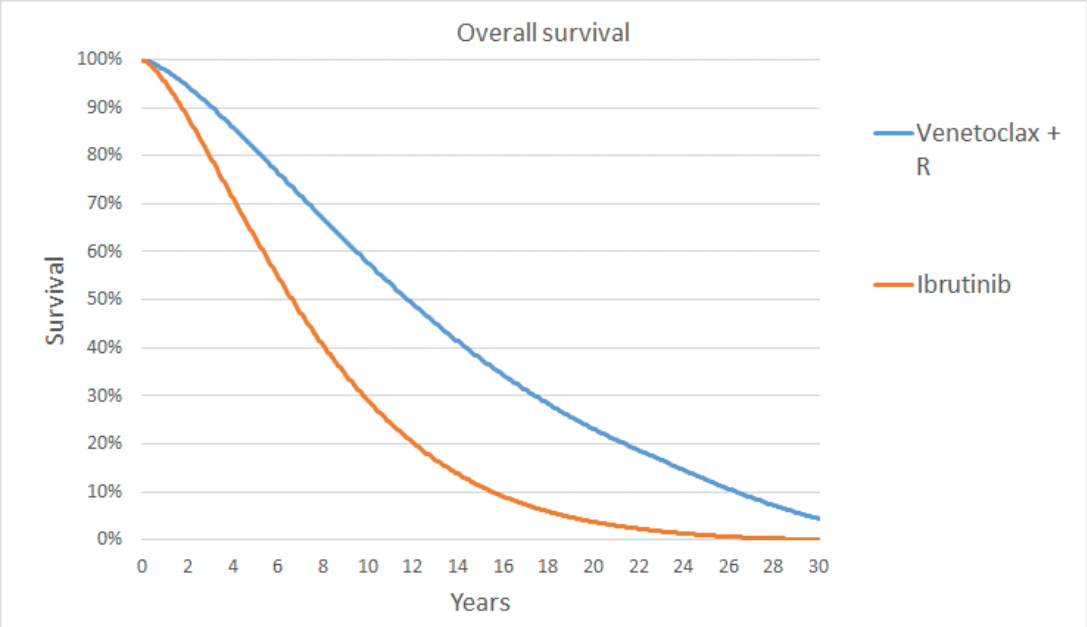


Figure 22 OS curves (VEN+R weighted towards RESONATE, Weibull model)



5. Analysis including utility values from the MURANO trial

Section 3.11, page 10 of the ACD states: "*The committee noted that there was a difference of 0.14 between pre-progression and post-progression utilities used in the economic model. It agreed that it would like to see an analysis including the utility values from the MURANO trial to gain a better understanding of the difference between the pre- and post-progression-free survival states and its impact on the cost-effectiveness analysis"*

As discussed in the ACD, the utility values from the MURANO trial appeared too high and implausible to use in the economic model. Therefore AbbVie took a conservative approach and used the committee and ERG's preferred utilities based on the TA487 venetoclax monotherapy appraisal - i.e. PFS utility value of 0.748 and post-progression survival (PPS) of 0.60 (difference of 0.148) from the literature. Notwithstanding, this section provides evidence that even when extreme differences between pre and post progression utilities are applied, VEN+R dominates ibrutinib in both list and net price comparisons.

Pre progression (i.e. PFS) utilities

The PFS utility value used in this analysis is the weighted average of the PFS utility values for VEN+R and BR computed from the MURANO trial EQ-5D – see table below.

Table 20 PFS utility values from MURANO EQ-5D

	VEN+R	BR	Weighted average
PFS utility values	0.855	0.824	0.840

Post progression (i.e. PPS) utilities

Although the MURANO trial collected EQ-5D assessments post progression (once at progression and once at the first assessment following progression) there were very few assessments available from the MAY 2018 data-cut. In fact, just 25 were available making up 0.5% of all EQ-5D responses available. Therefore, this data is not appropriate for the modelling of a health state utility value. However a scenario analysis is presented below whereby the difference between the MURANO trial PFS utility value and PPS utility value ranges from 0.24 to 0.5. The latter value of 0.5 difference between pre and post progression utilities represents an extremely pessimistic scenario and even with this pessimistic scenario, VEN+R dominates ibrutinib at list and net price.

Table 21 MURANO EQ-5D scenario analysis (with LIST and NET prices)

	VS. Ibrutinib (list prices)			VS. Ibrutinib (net prices)		
Diff. between pre and post-progression utility	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£)**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£)**
Base case (Literature, Dretzke – PFS:0.748, PPS:0.60) Difference = 0.148	[redacted]	**2.007**	**VEN+R is Dominant**	**-160,506**	**2.007**	**VEN+R is Dominant**
(MURANO - PFS:0.840) (Literature, Dretzke - PPS:0.600) Difference = **0.24**	[redacted]	2.068	VEN+R is Dominant	-160,506	2.068	VEN+R is Dominant
Difference: **0.3**	[redacted]	1.916	VEN+R is Dominant	-160,506	1.916	VEN+R is Dominant
Difference: **0.4**	[redacted]	1.665	VEN+R is Dominant	-160,506	1.665	VEN+R is Dominant
Difference: **0.5**	[redacted]	1.413	VEN+R is Dominant	-160,506	1.413	VEN+R is Dominant

NICE National Institute for Health and Care Excellence

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2018 **email:** TACommC@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[British Society of Haematology, Royal College of Pathologists]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Nil]
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	It is fair to say that the committee has considered all the evidence presented in front of them.
2	However, the recommendation implies that venetoclax with rituximab in the relapsed and refractory CLL is not an effective treatment option for this group of patients as compared to other available options. There is a clear benefit demonstrated in terms of deeper responses and progression-free survival as compared to chemo-immunotherapy arm based on the short follow-up and this has been recognised by the committee.
3	Comparison with B-cell receptor antagonist therapy is nearly impossible to make due to two reasons: One is the different mechanism of action of the drugs resulting in variable responses. B-cell receptor antagonist including ibrutinib and idelalisib invariantly result in partial responses in majority with only few patients achieving complete responses. MRD negativity is not achievable with this group of drugs. On the other hand, Venetoclax with rituximab achieves deeper remissions as well as MRD negativity. This make it very difficult to compare the two classes of drugs other than in a head to head comparison in a trial (Unlikely to happen). Secondly is the variation in the phase 3 trial population of various included studies that is manifested in the varied results of clinical and cost-effectiveness analysis. Hence, conclusions to draw degree of effectiveness or ineffectiveness with fixed therapy versus continuous therapy is very difficult.
4	It is a very sensible to review the data cut off at the later time point once patients have finished 2 years of venetoclax to establish the continued effectiveness of the treatment and we would agree with that entirely. The depth of response does matter in all venetoclax studies including Phase 1b venetoclax with rituximab study (Seymour et al) where patients achieving complete response and MRD negativity translated in longer disease-free relapse. If the later data cut-off suggests continued deep responses and very few relapses, it is hard to justify why this fixed duration therapy would not be beneficial to the patients.
5	As with any CLL study, the overall survival data will take time to mature and there are salvage treatments available especially in the chemoimmunotherapy arm which makes it difficult to make a short-term decision.
6	The economic analysis should be again considered based on the later cut-off data in order to make a better judgement on the continued effectiveness of the treatment and we would agree with that.
7	We would ask the committee to review the recommendation based on various points raised. This treatment opens a choice for our patients and gives us flexibility to treat our patients with a very effective treatment which does not at least appear inferior to other options available at present.
8	If NICE wants to wait for the data to mature then provision of this option on Cancer drug fund would be sensible which will allow us to accumulate real world data as well and may help in future recommendations.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Chronic Lymphocytic Leukaemia Support Association (CLLSA) and Lymphoma Action are supporting this submission
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We request that the updated and most recent clinical evidence from Prof Dr P Hillmen, that he offered at the Appraisal meeting, is fully considered as part of the appraisal consultation.
2	Equality issues will arise if Venetoclax plus Rituximab is not available for first relapsed patients. Restricting the target population to patients post chemo-immunotherapy excludes patients with del17p, TP53 mutation and those that were treated in a clinical trial (particularly FLAIR) who received Ibrutinib as first line treatment. Venetoclax plus Rituximab is a very important and effective treatment option for this group who have few treatment options and consequently a poor prognosis.
3	Due to the heterogeneous nature of the disease and the age range of patients, there is a need for access to multiple treatment options for relapsed/refractory patients with CLL. For relapsed patients with comorbidities, which may restrict their treatment options, Venetoclax plus Rituximab is a valuable and important effective option.
4	A fixed duration of treatment is both acceptable and welcome to CLL patients.
5	Venetoclax plus Rituximab offers increased remission rates with the potential of MRD negativity and hopefully prolonged survival with an acceptable safety profile. This is a substantial shift for the prognosis of relapsed CLL patients.
6	

Insert extra rows as needed

NICE National Institute for Health and Care Excellence

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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.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	We thank the committee for the opportunity to respond
1	**Decision by Appraisal Committee to not recommend venetoclax plus rituximab**. We are concerned about potential delays preventing patients and clinicians from accessing this treatment and do not agree with the ACD non-recommendation 1.1 of Venetoclax with rituximab use within its anticipated marketing authorisation, for treating relapsed or refractory chronic lymphocytic leukaemia in adults. European Commission approval was granted on 1st November for the use of this novel combination in this setting across all 28-member European states, Iceland, Liechtenstein and Norway. Additional data is now available providing 36 month follow up data in the ASH Murano study abstract publication https://ash.confex.com/ash/2018/webprogram/Paper118012.html The full study paper should be available to the ERG and committee from the company and will published publicly in early December at ASH 2018.
2	**Treatment choice.** CLL is a complex and varied disease. Most patients are in an older group living with many comorbidities which make current treatments unsuitable or intolerable. Repeated chemotherapy is not generally recommended today due to cumulative toxic side effects, intolerance or unsuitability. Today Ibrutinib is the current clinical standard of care for treating R/R patients and idelalisin plus rituximab as an alternative. Ibrutinib or idelalisib plus rituximab are associated with side effects that can exclude their use in a high proportion of R/R patients or are hard to tolerate by many over time. Venetoclax + rituximab has a favourable tolerability and toxicity profile and gives patients with comorbid, cardiac, anticoagulation and bowel issues an alternative to treatment with Ibrutinib or the alternative of idelalisib plus rituximab. Clinical choice is critical for clinicians to be able to tailor therapy and long-term treatment plans to the individual's health needs thereby ensuring survival and quality of life is maximised. Patients understand the limitations of therapies available as standard of care in this setting and that they do not come without serious risk of complication or long-term side effects. This is causing some considerable distress to many in this setting.
3	**Treatment sequencing and personal treatment plans.** In an era of developing personalised medicine CLL patients are becoming increasingly aware of the need for an appropriate tailored approach to their own treatment, rather than the dangers associated with a one size fits all approach. Patients and their clinicians require treatment options to fit with the increasingly complicated treatment landscape and treatment sequencing complexities, to ensure treatment continuity. Patients relapsing from a prior therapy require access to tolerable therapies that offer a chance of reaching MRD negativity early, followed by a treatment free period and improved quality of life. Patients worry they will not achieve enduring remissions or worry about side effects or toxicities of currently available options
4	**Important new treatment option** 3.1. We are pleased the committee concluded that venetoclax plus rituximab could be an important treatment option for people with relapsed or refractory chronic lymphocytic leukaemia and pleased that 36 month cut off data confirms the durability of responses to this therapy.
5	**Clinical effectiveness.** We are pleased the committee concluded that the clinical-effectiveness 3.3, 3.4 was relevant to NHS clinical practice in England. At 23.8 months of venetoclax treatment about 60% of patients in the trial had negative minimal residual disease status, which is "a strong predictor of lasting remission in patients with chronic lymphocytic leukaemia". We are pleased to see that 36 month data shows few patients progressing after the 2-year therapy.
6	**Suitability for Cancer Drugs Fund.** We are very concerned that early access to this urgently needed treatment is being delayed and do not agree with the ACD conclusion and reasoning 3.16 that venetoclax plus rituximab is not suitable for the Cancer Drugs Fund. We are hopeful that the company will ensure that they have now properly addressed the ERG, appraisal committee and NHSE concerns. We hope 36 month trial cut off data analysis will enable use of correct hazard ratios in modelling to reflect the fixed duration of venetoclax treatment. Early access through the Cancer

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2018 **email:** TACommC@nice.org.uk/NICE DOCS

	Drugs Fund will help meet an urgent area of unmet need and fill a therapeutic void for relapsed patients.
	Loss of treatment effect. We understand that potential loss of treatment effect after 2 years with venetoclax plus rituximab was not reflected in the original analysis. 3.10 However we are pleased that recently published 36 months cut off data enables modelling to be created that will reduce uncertainties that arose from the original modelling at 23.8 months. This should now strengthen modelling extrapolations, making ICER calculations more robust. We are hopeful that this latest available data will enable the company and ERG to remodel comparisons and data to effectively satisfy requirements for CDF inclusion.
	Additional treatment benefits. We are concerned that the committee believes that there are no additional benefits that are not captured in the cost-effectiveness analysis, despite expressing the belief that the new treatment is beneficial for patients. 3.14. Patient groups have presented feedback of patient experience with the treatment and outcome improvements. We believe that making this treatment available via the CDF will enable uncertainties to be addressed and patient reported outcomes to be collected, strengthening the data on the benefits to patient quality of life.
	Treatment step change and innovation. Venetoclax plus rituximab offers a step change in treatment strategy. Venetoclax plus rituximab gives patients a chance of a achieving a preferred treatment break, and enduring remission, without the complications and side effects caused by a continuous therapy or very myelotoxic chemoimmunotherapy (CIT). Many cannot tolerate or are not suitable for retreatment with a CIT or with continuous therapies such as ibrutinib & idelalisib plus rituximab, due to comorbidities and side effects associated with these current standards of care.
	Patient experience. In our CLL patient experience survey, patients were asked, 'Would you consider it positive if a treatment plan contained a treatment-free period or included stopping treatment altogether?'– analysis of responses confirms that patients prefer a treatment-free period or prefer being able to stop treatment altogether. Venetoclax plus rituximab provides a treatment free interval after a defined 2-year treatment period, the majority are achieving MRD negativity and are still in remission at 36months.
	Health economics. We believe that venetoclax plus rituximab as a 2-year limited treatment therapy has plausible potential to be cost-effective versus the current standard of care. More recent trial data when used in health economic evaluations confirms favourable ICER rates for Ven+R compared to comparators. We request the committee reconsider their original decision and make this treatment available through the Cancer Drugs Fund. Continued data collection through CDF will remove uncertainties without denying patients in the relapsed setting an effective therapy approved for European prescribing.

Insert extra rows as needed

Letter on behalf of the UK CLL, the voice of the broader community of clinicians, scientists, nurses and patients.

Thank you very much for giving us the opportunity to comment on the recent Venetoclax & Rituximab technology appraisal as a therapy for patients with relapsed CLL.

As clinicians and CLL specialists, we feel strongly that patients with relapsed CLL should be given a choice of therapies. This is primarily because of the fact that two-thirds of patients will have other significant co-morbidities that influence the choice of optimal therapy.

What are the options?

1. **Evidence of the (non)-efficacy and toxicity of retreatment with chemoimmunotherapy in previously treated CLL patients**

I refer to our review of this option from August of this year following the TIMES letter regarding access to Ibrutinib for patients relapsing within three years of chemoimmunotherapy. As a result of this option appraisal, NHSE accepted the evidence against repeat CIT at relapse and changed the Bluetec inclusion criteria in favour of Ibrutinib.

Retreatment with BR

The first study evaluating Bendamustine and Rituximab systematically for the treatment of relapsed CLL showed a median PFS of 15.2 months for BR at 24 months follow-up[1]. At the time, Ibrutinib was not available and therefore the study included patients with fludarabine-refractory CLL and also patients with deletions of chromosome 17p. Toxicities were mainly haematological and affected 25% of patients overall.

The Helios study compared Ibrutinib with bendamustine and rituximab with placebo, bendamustine and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma[2]. Patients who had relapsed early after chemoimmunotherapy (i.e. within two years) were excluded. 48% of patients recruited had received only one prior line of therapy. In addition, patients had to be fit enough to tolerate further chemoimmunotherapy with BR. With a median follow-up of 17 months, the median PFS for Ibrutinib (plus BR) treated patients was not reached compared to 13.3 months for those treated with BR only. At 18 months, 79% of patients in the Ibrutinib treated group had not relapsed versus 24% of patients treated with BR. The most common Grade 3 or 4 side-effects were neutropenia and thrombocytopenia. These occurred in about 50% of patients in both arms and were attributed to BR. Infections were seen in about 10% of patients in both arms.

These data confirm the results from the Murano study[3] that had very similar inclusion/exclusion criteria to Helios and recruited mostly patients who had only one prior line of therapy and showed a median PFS of 17 months for BR-treated patients. The risk of Grade 3 or 4 neutropenia was 51 and 39% for Helios and Murano, respectively.

Importantly, bendamustine was withdrawn from the CDF for relapsed CLL when Ibrutinib was NICE approved in 2016.

Re-treatment with FCR or other multi-agent chemoimmunotherapy

The LUCID study[4] used FCR as the control arm. 62% of patients recruited had undergone only one prior line of therapy, 58% had received fludarabine containing regimen, the others had received less effective chemotherapy or chemoimmunotherapy. The median PFS of the FCR treated control cohort was 24 months. 40% of patients had a serious adverse event, mainly due to infection related hospital admissions. 5% of patients died and the discontinuation rate was 30%. Together, these data clearly indicate that FCR in the relapsed setting lacks efficacy and has significant toxicity.

The REACH study[5] compared FC against FCR. Patients with prior exposure to FCR were excluded. Despite that, the PFS of FCR treated patients was only 30 months. Importantly, 89% of patients presented with Grade3 or 4 neutropenia and the treatment-related death rate was 7%.

Neiderle et al compared BR and FCR in patients relapsing after frontline therapy with alkylating agents[6]. Patients who had received prior treatment with bendamustine or fludarabine were excluded. Despite this, the PFS was less than two years in both arms and not statistically different between the two arms.

Other studies evaluating multi-agent chemoimmunotherapy in the relapsed setting are the MDACC single centre observational study[7] and the French Collaborative groups[8]. Both included patients with prior exposure to FCR. Re-treatment regimen were more heterogenous (FCR, BR, alemtuzumab, CHOP-R etc), but the median PFS was under 2 years[1,7,9].

Importantly, multiagent chemoimmunotherapy, in particular FCR is associated with an increased risk of second cancers and AML. In the largest series reported, the risk of second cancers was 2.38 times higher than the expected risk in the general population. The rates for t-AML/MDS (5.1%) was also high[10].

Up until now, the evidence in favour of using the targeted agents (Ibrutinib, Idelalisib, Venetoclax) instead of CIT in the relapsed setting -although compelling- , has been based on “across trial” comparisons (see above). The Murano study is the first to compare a targeted agent directly against current best available chemoimmunotherapy.

2. Treatment with Ibrutinib or Idelalisib: a One-size-fits-all-model for patients with relapsed CLL is dangerous

One of the arguments currently used in the TA is that Ibrutinib and Idelalisib are already NICE approved for patients with relapsed CLL and that it is not clear what the VR combination would add.

2.1 We refer to the MHRA routine European review that examined the safety profile of ibrutinib (https://www.gov.uk/drug-safety-update/ibrutinib-imbruvica-reports-of-ventricular-tachyarrhythmia-risk-of-hepatitis-b-reactivation-and-of-opportunistic-infections).
In this meta-analysis of all Ibrutinib trials, an excess death rate due to cardiac toxicities was found in addition to an increased risk of hepatitis B reactivation and a significant risk for opportunistic infections. As a result, the MHRA asked the company to update the patient information and to include:

a. ventricular tachyarrhythmia including sudden cardiac death as a common adverse reaction (<10 in 100 patients)

b. hepatitis B virus reactivation as an uncommon adverse reaction

Importantly, clinicians were advised to withhold Ibrutinib in patients with symptoms that could be due to arrhythmia, and patients who are particularly vulnerable to opportunistic infections, such as patients with pre-existing lung disease, should be considered for alternative therapies and started on prophylaxis.

In addition to these life-threatening complications, 16% of patients on Ibrutinib will develop atrial fibrillation and need anticoagulation with NOACs (warfarin is contra-indicated) further adding to co-morbidities and cost of CLL treatment.

2.2 Idelalisib
The committee is aware of the increased risk of immunogenic side-effects relating to PI3K inhibitors such as Idelalisib with 20% of patients developing treatment-related colitis or pneumonitis that leads to permanent discontinuation of therapy. Idelalisib use is therefore restricted to patients who are intolerant to Ibrutinib. However, the number of patients intolerant to both drugs is increasing as we begin to learn more about the long-term side-effects of Ibrutinib.

3. Venetoclax &Rituximab

The Murano study shows that the VR combination is **safe and well tolerated** and would therefore represent a significant step-change in the choice of therapies available for our patients, especially for the significant number of patients with a previous history of cardiac or pulmonary disease. The VR combination achieves an **unprecedented rate of MRD negativity** convincingly showing its superiority with respect to efficacy compared to CIT. Moreover, patients find the **fixed duration** of therapy highly attractive.

Importantly, patients with **treatment-naïve TP53-disrupted CLL** should also have a choice (ibrutinib or venetoclax & rituximab), and patients with **relapsed TP53-disrupted CLL** should be given access to the same (superior) treatment of venetoclax in combination with rituximab instead of venetoclax only (current treatment) as the TP53 wildtype patients.

Finally, we note the committee is concerned there may be loss of treatment effect after 2 years of VR when treatment is discontinued. However, we note that the latest MURANO data to be presented at ASH 2018 in 2 weeks from now is not suggestive of such a loss of effect, as the PFS in the latest analysis in patients who completed 2 years of treatment remains excellent at 92% and 87% at 6 and 12 months respectively. This implies continued remissions in patients off treatment.

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Table 2: Summary of relapsed-refractory RCTs in CLL

Name of Study	Study	Arms	Prior therapy	Median age (years)	Number of Patients	ORR	CR	Median follow-up (months)	PFS (months)	OS (months)	N'penia (≥ grade 3)	Pneumonia (≥ grade 3)
"Fischer" Phase 2	**Fischer K. et al (2011)**	BR	1-3 prior therapies	66.5	78	59%	9%	24	15.2	33.9	10.2%	12.8% (infections)
REACH	**Robak T. et al (2010)**	FC	Prior therapy with FCR excluded	62	276	58%	13%	25	20.6	NR	84%	6%
		FCR		63	276	69.9%	24.3%		30.6	NR	89%	5%
HELIOS	**Chanan-Khan A. et al (2016)**	BR + Ibrutinib	Relapse within </=2 years from chemo excluded	64	289	83%	10.4%	17	NR	NR	54%	7%
		BR		63	289	68%	2.8%		13.3	NR	51%	1%
NONE	**Neiderle N. et al (2013)**	BR	After 1st line therapy only	68	49	76%	27%	34	20.1	43.8	35%	U
		FR		69	43	62%	9%		14.8	41.0	30%	U
LUCID	**Awan F.T. et al (2014)**	FCR+lumiliximab	At least 1 but not more than 2 prior lines	61	316	72%	16%	*	24.6	NR	72%$	5%
		FCR		61	311	61%	15%		23.9	NR	71%$	8%
		Ibrutinib		67	195	63%#	2%	9.4	NR	NR	16%	7%

RESONATE	**Byrd J.C. et al (2014)**	Ofatumumab	Patients with remissions >3 years excluded	67	196	4%#	0%		8.1	NR	14%	5%
RESONATE update	**Brown JR et al (2018)**	Ibrutinib	Patients with remissions >3 years excluded	67	195	90	7	19 (max: 26)	NR	NR	19.5 (cumulative)	12.4 (cumulative)
		Ofatumumab		67	196	25	1.5% (cross over)		8.1	NR (cross over)	NA	NA
GS-0115	**Zelenetz A.D. et al (2017)**	BR+ idelalisib	Patients with remissions >3 years excluded	62	207	70%	1	14	20.8	NR	59%	10%
		BR+placebo		64	209	45%	0		11.1	31.6	47%	8%
MURANO	**Seymour J.F et al (2018)**	Venetoclax +Rituximab	1-3 prior therapies; at least 2 years remission	65	194	93%#	27%#	24	NR	NR	58%	8%
		BR		66	195	67%#	8%#		17	NR	39%	8%

#independently assessed responses; $ grade 3 neutropenia and leucopenia reported together in this study; *trial halted after 2nd interim analysis at 33 weeks

ORR overall response; CR complete response; PFS progression free survival; OS overall survival; BR bendamustine & rituximab; FR fludarabine & rituximab; NR not reached; U unreported

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Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Consultation on the appraisal consultation document – deadline for comments 5pm on 16 November 2018 **email:** TACommC@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gilead Sciences
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Section 3.2 We request that the following statement is clarified and amended: *'This is because idelalisib plus rituximab has an intensive dosing regimen, and is associated with an increased risk of infection'* We do not agree that idelalisib plus rituximab should be regarded as a more intensive dosing regimen. Physicians familiar with the treatment of chronic lymphocytic leukaemia (CLL) and the use of idelalisib will be aware of the use of prophylactic medication to minimise the risk of treatment-related infections. The occurrence of treatment-related infections has also been described with the use of other treatments for relapsed or refractory CLL such as ibrutinib.
2	We would like to draw the committee's attention to the growing body of evidence which postulates the potential benefit of using venetoclax as a later, rather than earlier line of therapy in CLL. For example, Deng et al. demonstrate that use of Bruton's tyrosine kinase inhibitors may increase BCL2 dependence of CLL cells, possibly enhancing the use of venetoclax when used as a later line of therapy, after treatments such as ibrutinib. Relevant references include: - Carter MJ et al. 2017. Leukemia 31, 1423-1433 (https://www.nature.com/articles/leu2016333) - Deng J et al. 2017. Leukemia. 2017 Oct;31(10):2075-2084 (https://www.ncbi.nlm.nih.gov/pubmed/28111464)

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Janssen-Cilag**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	Comments

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1	Janssen thank NICE for the opportunity to comment on the preliminary decision after the consideration of the evidence for venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia. We believe that all relevant evidence has been taken into account however, we would like to comment on Section 3.5 of the document. Section 3.5 of the ACD discusses the committee's consideration of the MAIC presented by the manufacturer: *"The ERG also noted that patients had not been matched correctly, making the population in the RESONATE trial (ibrutinib) appear healthier than the population in the MURANO trial (venetoclax plus rituximab). This meant that the benefit of ibrutinib may have been underestimated."* Janssen believe the effectiveness of ibrutinib has been underestimated in the manufacturer's analysis. We agree that the incorrect matching along with other methodological choices cause the underestimation. The company did not adjust for important treatment effect modifiers such as number of prior therapies and percent of patients who are purine-analogue refractory. This is supported by the NICE DSU Technical Support Document 18. 1. National Institute of Health and Care Excellence. DSU Technical Support Document 18: Methods for Population-adjusted Indirect Comparisons in Submissions to NICE. Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf.

Professor Peter Hillmen
University of Leeds,
Section of Experimental Haematology,

16th November 2018

Ms Stephanie Callaghan
Project Manager, Technology Appraisals – Committee C
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza,
Manchester M1 4BT

Dear Ms Callaghan

Re: Venetoclax with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

Thank you for sending through the draft ACD for venetoclax plus rituximab. I am obviously disappointed in the conclusion and hope with a review of the further information that is being submitted this might change. Specifically regarding the draft ACD I have listed my comments in red below.

Page 3:

"1.1 Venetoclax with rituximab is not recommended, within its anticipated marketing authorisation, for treating relapsed or refractory chronic lymphocytic leukaemia in adults." *It is difficult to understand why such an important combination with over half of patients with relapsed CLL achieving MRD negative remissions with a fixed duration of therapy cannot be better than continuous therapy until resistance to therapy. The further follow-up of MURANO to 3 years indicates that stopping venetoclax therapy is safe.*

"Relapsed or refractory chronic lymphocytic leukaemia is currently usually treated with ibrutinib. Clinical trial evidence suggests that venetoclax plus rituximab increases how long people live for before their disease gets worse compared with bendamustine plus rituximab (a combination that is rarely used now). Indirect comparisons of venetoclax plus rituximab with ibrutinib have limitations, so no firm conclusions can be drawn about the size of the benefit for venetoclax plus rituximab." *Both venetoclax (±rituximab) and ibrutinib are proven to be more effective than chemoimmunotherapy in relapsed CLL. The two drugs work in different and complementary ways and it is clear that patients crossing over from one drug to the other are likely to respond again. It does not seem logical to deny patients treatment with venetoclax plus rituximab because ibrutinib is effective. In fact it is important that both therapies are available for patients with the choice of sequencing being determined by patient choice or on cost pharmaco-economic criteria.*

"For example, there are inconsistencies between the clinical- and cost-effectiveness data used because the costs of venetoclax treatment last for 2 years but the benefits continue for more than 2 years." *This is difficult to follow. How can stopping a therapy at 2 years with continued benefit beyond that point be a bad thing to happen. Maybe the pharmaco-economic model needs refining but it must be a good thing both for patients and economically!*

Page 5:

“It concluded that venetoclax plus rituximab could be an important treatment option for people with relapsed or refractory chronic lymphocytic leukaemia.” *Clearly venetoclax plus rituximab **is** an important treatment option in relapsed or refractoy CLL.*

Page 7:

“It concluded that, although venetoclax plus rituximab was clinically effective compared with bendamustine plus rituximab, the immaturity of the data raised uncertainty, and that more recent data from the trial would be welcomed.” *The median follow-up in the MURANO Trial as submitted was significantly longer than the median PFS of the comparator (bendamustine plus rituximab [BR]) and therefore there is no “uncertainty” over the conclusion that venetoclax plus rituximab is significantly better than BR.*

3.5 “This was because the hazard ratio estimate for progression- free survival was higher than the estimate for overall survival, which was not the case in the comparator trials. The clinical experts stated that the overall survival hazard ratio estimate was not plausible whereas the progression-free survival estimate was.” *As pointed out in the meeting a reason why the HR might be larger for PFS compared to OS for venetoclax plus rituximab in the MAIC to ibrutinib is that patients were who relapsed after VR in MURANO were able to receive ibrutinib, thus improving survival, whereas in the ibrutinib trials (RESONATE) patients could not cross over to venetoclax which was not available at the time.*

Page 9:

3.10 “It noted that there were no data from MURANO on the effect of implementing the stopping rule because the data cut was based on a median follow-up of 23.8 months.” *In the report there was some data on stopping venetoclax at two years as some patients were at 36 months of follow-up. There was very little fall in the Kaplan-Meier survival curve beyond 24 months. This is supported by the further follow-up of the trial in the latest data-cut.*

I really hope that the decision not to fund the combination of venetoclax plus rituximab in relapsed CLL can be overturned.

Yours Sincerely,

Professor Peter Hillmen
Consultant Hematologist and Professor of Experimental Hematology

Appendix 2

Addendum

Additional evidence provided in response to Appraisal Consultation Document (ACD)

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]

November 2018

FURTHER SCENARIOS RELATED TO THE COST COMPARISON REQUESTED BY THE COMMITTEE

Section 3.13, page 12, of the ACD states "*The committee noted comments from the clinical experts that venetoclax plus rituximab has similar, or better, efficacy to ibrutinib (see section 3.5). It agreed that, because of uncertainties in the company's modelling, a cost comparison of venetoclax plus rituximab and ibrutinib is requested from the company, which might address these uncertainties*"

Based on the assumption that VEN+R and ibrutinib have equal efficacy (i.e. PFS and OS HRs of 1), a cost comparison was provided to NICE (see Appendix 1) on 16th November 2018. The cost comparison of VEN+R vs ibrutinib assuming equal efficacy demonstrated that VEN+R is substantially lower in cost compared to ibrutinib. No post-progression treatment costs were included for either regimen.

On 21st November 2018, NICE informed AbbVie that the committee chair requested "*that the cost comparison analysis should also include scenarios accounting for the cost of subsequent treatment with ibrutinib after people have completed 2 years therapy with venetoclax plus rituximab. Since the number of patients who need to continue therapy with ibrutinib is uncertain, the committee chair suggested that the scenario analysis should include the cost of treating 100%, 50% and 30% of patients with ibrutinib after completing 2 years treatment with venetoclax plus rituximab*".

AbbVie has undertaken the analyses requested by NICE and the results are presented below. However, it should be noted at the outset that assuming patients will go on to receive ibrutinib immediately, irrespective of whether they have progressed, is a clinically implausible scenario, which is not supported by the MURANO trial data and there is no evidence of clinical support for this approach. There is evidence that on completion of the two year fixed treatment duration most patients are treatment free. Furthermore, in the MURANO trial (May 2018 data cut) the rate of CLL progression in the first 12 months after venetoclax fixed treatment duration completion was modest (13%).

The analyses below show that in almost all cases, VEN+R is lower in cost compared to ibrutinib. The only scenario when ibrutinib is marginally lower in cost compared to VEN+R is when an assumption is made that 100% of patients completing 2 years of VEN+R treatment go on to ibrutinib, irrespective of whether they have progressed.

Scenario Method

The cost comparison in the following section is augmented by making a large deviation from the MURANO treatment protocol for VEN+R. Instead of patients stopping treatment after the 2-years fixed treatment duration, patients switch to receive ibrutinib until progression. The switching factor is set to 100%, 50% and 30%. This is included in the cohort model by making an adjustment to the per cycle cost of ibrutinib i.e.

- 100% switch = £4292.40
- 50% switch = £2146.20
- 30% = £1287.72.

1. Cost comparison- 100% of VEN+R patients receive Ibrutinib after FTD

Table 1 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 1 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with LIST prices)

Table 2 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 2 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

2. Cost comparison- 50% of VEN+R patients receive Ibrutinib after FTD

Table 3 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 3 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with LIST prices)

Table 4 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 4 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

3. Cost comparison- 30% of VEN+R patients receive Ibrutinib after FTD

Table 5 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 5 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with LIST prices)

Table 6 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: VEN+R, Venetoclax+Rituximab; Idela+R, Idelalisib+Rituximab; PFS, Progression Free Survival; PPS, Post Progression Survival; AE, adverse event.

Figure 6 Cost comparison between VEN+R and Ibrutinib assuming PFS/OS HR=1 (with NET prices)

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]:

ERG Response to New Company Evidence

Produced by: Warwick Evidence

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Declared competing interests of the authors

None

Summary points:

- Considerable uncertainty remains in the incremental costs and effects of the comparison of venetoclax-rituximab (VEN+R to ibrutinib.
- Active treatment costs beyond initial course of VEN+R therapy are not considered for patients on VEN+R arm.
- Whilst patient options remain unclear, substantial additional costs could be introduced onto both arms, though a bigger impact is expected on the VEN+R arm.
- It is unclear to the ERG what factors will influence a patients options, (e.g. undetectable minimal residual disease (uMRD) status, uMRD duration), and how these might affect patient performance.
- Treatment waning is implemented as a percentage increase on the hazard of the VEN+R arm, and without a reference point, so all scenarios explored have been chosen arbitrarily and may not be representative of a true waning effect.

Comments on additional follow-up of MURANO

The company submitted additional analysis which used data from additional follow-up of the MURANO trial (median 36 months follow-up compared with 23.8 months of previous submission). The ERG accept that the additional follow-up further demonstrates the greater efficacy of VEN+R compared to BR. It is worth reiterating that BR is neither the approved comparator in the scope nor is it licensed for treating relapsed/refractory CLL. For PFS and OS, the benefits are similar to the previous HR estimates, with the treatment effect in PFS slightly increasing, and slightly decreasing in OS (Table 1). As these HR are based on the entire follow-up period, it is difficult to assess whether there is any waning of the treatment effect based on the extended follow-up. HRs presented for every 6 months of follow-up would help detection of potential effect waning. For the uMRD outcome, there is a noticeable drop in both arms from 9 months to 24 months. The ERG are unsure whether the company has data on MRD at 36 months, but are concerned that this decrease may be evidence of a lack of sustained treatment effect of VEN+R, suggesting patients will require additional active treatment. There were no changes to the safety profile of the interventions.

Table 1: MURANO Hazard Ratio and uMRD Comparison for VEN+R vs BR

	AC1	AC2
PFS Hazard Ratio (95% CI)	0.19 (0.13, 0.28)	0.16 (0.12, 0.23)
OS Hazard Ratio (95% CI)	0.48 (0.25, 0.90)	0.50 (0.30, 0.85)
uMRD in VEN+R	62% (at 9 months)	48% (at 24 months)
uMRD in BR arm	13% (at 9 months)	2% (at 24 months)

Comments on Economic Analysis

The company submitted five sets of analyses, addressing concerns previously voiced by the committee. Note that all ICERs presented by the company and in this document do not include the costs of later lines of active treatment, or the CAA discount on ibrutinib. A separate appendix presents analyses using the ibrutinib CAA discount. Recall VEN+R is taken until disease progression, unacceptable toxicity for a maximum of 2 years, and ibrutinib is taken until disease progression or unacceptable toxicity. The ICERs in this document all have the CAA of venetoclax included. (i.e. net price)

The company used a joint Weibull distribution to model PFS and OS, as they had done previously, but without providing any assessment of whether this was suitable given the new data available. The ERG assessed the long term OS predictions and note that the company's choice of Weibull has changed from predicting [redacted] of patients alive at 20 years to [redacted] with the new evidence. The ERG's original choice was gamma, which has increased from [redacted] to [redacted] at 20 years, which the ERG believe may now be too optimistic. The ERG's preferred parametric model is the generalised gamma as the predictions are most consistent with expert opinions expressed in the previous ERG report, though other parametric models also give plausible extrapolations (Weibull, log-logistic and gamma).

Table 2: OS extrapolation comparison

OS AC2			**Exponential**	**Gen Gamma**	**Weibull**	**Log-logistic**	**Gamma**	**Log-normal**
AIC			Not provided					
VEN+R OS New Evidence	**Median (years)**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Survival %	**2-year**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS AC1			**Exponential**	**Gen gamma**	**Weibull**	**Log-logistic**	**Gamma**	**Log-normal**
AIC			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R OS	**Median (years)**		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Survival %	**2-year**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		5-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		10-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		20-year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The issues that the ERG found with original submission are still present, with the company's base case analysis using the results of the MAIC. The MAIC results remain implausible with greater benefit for VEN+R over ibrutinib predicted for OS than PFS. The ERG maintained their preference for

estimating relative treatment effects of ibrutinib using their NMA, and information from the Hillmen abstract. Whilst an updated hazard plot has not been provided by the company, the ERG believe the joint modelling of PFS and OS from the MURANO trial still results in poor representation of the OS data for VEN+R in the economic model (Figure 4 of previous ERG report).

Table 3: Base Case Hazard Ratio Comparison of VEN+R vs Ibrutinib

	AC1	AC2
MAIC adjusted PFS Hazard Ratio (95% CI)	[redacted]	[redacted]
MAIC adjusted OS Hazard Ratio (95% CI)	[redacted]	[redacted]
NMA PFS Hazard Ratio (95% CI)	[redacted]	[redacted]
NMA OS Hazard Ratio (95% CI)	[redacted]	[redacted]

The ERG noted the differences between progression free survival and post-progression survival derived from the company's base case analysis (Table 4). It is apparent that patients on VEN+R have a much higher post progression survival, but the ERG are not aware of any clinical evidence or reasoning to support this result, particularly if no later lines of treatment are received. Alternatively, the ERG's base case yields post-progression survival estimates that are more consistent across both comparators.

Table 4: Undiscounted LY estimates of ibrutinib

	HR Source	**IBRU PFS LY**	**IBRU PPS LY**	**IBRU Total LY**	**VEN+R PFS LY**	**VEN+R PPS LY**	**VEN+R Total LY**
Company Base Case AC2	Company MAIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Base Case AC2	ERG NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The first analysis was a cost comparison, where equal efficacy was assumed between VEN+R and ibrutinib. The ERG were able to reproduce the results provided by the company, and repeated the analysis using the generalised gamma parametric model. Under the assumptions, VEN+R appears to be cheaper than ibrutinib. The ERG repeated the analysis, using their preferred parametric fit (Table 5).

Table 5: Cost Comparison Results

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Company (Weibull)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Gen Gamma)								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The second analysis was the company's base case (Table 6), using updated MAIC results to reflect the newly available data. The company did provide accompanying sensitivity analyses, however the ERG were unable to attempt to replicate them and cannot comment on their accuracy. Given the underlying assumptions made by the company across the sensitivity analyses, the ERG are unsurprised to see that the sensitivity analyses all conclude that VEN+R dominates ibrutinib, and feel that they may not accurately capture the uncertainty in this comparison.

We believe the company made a mistake when reporting the LYG in their base case, however the QALY and ICER are correct. We have placed the correct values in Table 6. In the company's analysis, VEN+R appears to be both cheaper and more effective than ibrutinib. In the ERG's base case, VEN+R is cheaper, but less effective than ibrutinib.

Table 6: Base Case Results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company Base Case (Weibull + MAIC)							
Ibrutinib	[redacted]	6.25	4.35	-	-	-	-
VEN+ R		9.68	6.37	-£160,506	3.426	2.007	VEN+R is Dominant
ERG Base Case (Gen Gamma + NMA)							
Ibrutinib	[redacted]	10.19	6.33	-	-	-	-
VEN+R	[redacted]	9.69	6.68	-£228,230	-0.494	-0.351	£651,136

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years;

The third set of analyses expanded the company's base case analysis and explored waning the effect on VEN+R after 2 years. The range chosen by the company ranged from 5% to 40%, and each increases year after year. This may not accurately reflect a plausible waning effect, as the ERG suspect it may underestimate any short term waning, and overestimate any long term waning. The ERG do not necessarily agree with the company's comment that any waning would already be

captured in the model, as the parametric models are fitted to the whole follow-up period and may not reflect any waning that may be present in the tail, where there are fewer events and less follow-up. The ERG were unable to replicate the company's waning effect on the company's base case analysis, being unable to match either the VEN+R costs or QALYs reported by the company. However, when the ERG attempted to replicate them, VEN+R remained dominant. The ERG chose to implement the waning effects equally on PFS and OS onto the ERG base case analysis.

Table 7: Treatment Waning Comparison

		Costs	**QALYs**	**Inc Costs**	**Inc QALYs**	**ICER**
Company Base Case with 5% Waning*						
	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R		5.736	-£164,238	1.387	VEN+R is Dominant
Company Base Case with 10% Waning*						
	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R		5.367	-£166,369	1.018	VEN+R is Dominant
Company Base Case with 20% Waning*						
	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R		4.918	-£168,810	0.570	VEN+R is Dominant
Company Base Case with 30% Waning*						
	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R		4.640	-£170,241	0.291	VEN+R is Dominant
Company Base Case with 40% Waning*						
	Ibrutinib	[redacted]	4.349	-	-	-
	VEN+ R		4.444	-£171,216	0.095	VEN+R is Dominant
ERG Base Case with 5% Waning						
	Ibrutinib	[redacted]	6.682	-	-	-
	VEN+ R		6.231	-£228,727	-0.451	£507,379
ERG Base Case with 10% Waning						
	Ibrutinib	[redacted]	6.682	-	-	-
	VEN+ R		6.136	-£229,206	-0.546	£419,799
ERG Base Case with 20% Waning						
	Ibrutinib	[redacted]	6.682	-	-	-
	VEN+ R		5.960	-£230,113	-0.723	£318,471
ERG Base Case with 30% Waning						
	Ibrutinib	[redacted]	6.682	-	-	-
	VEN+ R		5.799	-£230,955	-0.883	£261,599
ERG Base Case with 40% Waning						
	Ibrutinib	[redacted]	6.682	-	-	-
	VEN+ R		5.653	-£231,735	-1.029	£225,189

* indicates analysis was attempted but could not be replicated by ERG, and results are taken from company new evidence report.

The fourth analysis presented by the company was based on patient characteristics of the RESONATE trial, to which the VEN+R patients were matched to in the company MAIC. Methodologically, this is

better use of the HR from the MAIC than the company base case, as this should match the population that the HR was calculated from.

The company did not report exactly how they implemented this analysis within the economic model. This meant the ERG were unable to verify the analysis, or to adjust it in any way. The company only provided a discussion of the methods for survival extrapolation, and did not comment on whether the baseline characteristics of the population in the economic model were changed.

The ERG are concerned that the company modelled the survival of the unadjusted MAIC population rather than the adjusted population, following the company's comments on the number of patients modelled. If the unadjusted population was used, then this includes patients from MURANO who met the inclusion criteria of RESONATE, but were not actually matched on their baseline characteristics. Without greater description from the company, the ERG is unclear of the relevance of these analyses.

The fifth analysis used utility values from the MURANO trial, which had been deemed unsuitably high for use in a base case analysis by the company and ERG previously. The company could not obtain a reliable utility estimate for post-progression survival due to a lack of available data, and instead explored a range of potential values, whilst maintaining the pre-progression utility value from MURANO.
When replicating the company's analyses, the ERG obtained marginally different estimates of QALYs, which are provided in Table 8. The ERG also replicated the scenarios based on the ERG base case analysis. The results of both sets of analyses do not appear sensitive to the preference of utility values.

Table 8: Results of analysis using alternative utility values.

	Pre Progression	Post Progression	Difference	Sources	Inc Costs + QALYs	ICER
Base Case	0.748	0.600	0.148	Pre: NICE TA359 Post: Dretzke 2010	-£160,506 2.007	Domin
Scenario 1	0.840	0.600	0.240	Pre: MURANO Post: Dretzke 2010	-£160,506 2.069	Domin
Scenario 2	0.840	0.540	0.3	Pre: MURANO Post: Diff 0.3	-£160,506 1.918	Domin
Scenario 3	0.840	0.440	0.4	Pre: MURANO Post: Diff 0.4	-£160,506 1.666	Domin
Scenario 4	0.840	0.340	0.5	Pre: MURANO Post: Diff 0.5	-£160,506 1.415	Domin
ERG Base Case	0.748	0.600	0.148	Pre: NICE TA359 Post: Dretzke 2010	-£228,230 -0.351	£651,136
Scenario 1 ERG	0.840	0.600	0.240	Pre: MURANO Post: Dretzke 2010	-£228,230 -0.398	£573,364
Scenario 2 ERG	0.840	0.540	0.3	Pre: MURANO Post: Diff 0.3	-£228,230 -0.402	£567,692
Scenario 3 ERG	0.840	0.440	0.4	Pre: MURANO Post: Diff 0.4	-£228,230 -0.409	£558,483
Scenario 4 ERG	0.840	0.340	0.5	Pre: MURANO Post: Diff 0.5	-£228,230 -0.415	£549,569

Venetoclax in combination with rituximab for treating relapsed or refractory chronic lymphocytic leukaemia [ID1097]:

ERG Response to Company Addendum

Produced by: Warwick Evidence

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Declared competing interests of the authors

None

The company provided an addendum where it investigated the possibility of VEN+R patients taking ibrutinib following completion of the two year course on venetoclax. The company notes that it is implausible to assume that all patients would receive ibrutinib regardless of their progression status. The ERG agree and suggest uMRD history may also influence a decision on later treatment. The ERG are unsure whether there is any potential for a patient to begin a new course of VEN+R if they previously achieved uMRD but relapsed after the initial two-year treatment course.

The ERG agree that the assumption that all patients finishing VEN+R immediately take ibrutinib is not supported by evidence, however there is a general paucity of evidence on this matter. The company's analysis assumes that patients in the VEN+R arm who are progression-free will take ibrutinib following their course of venetoclax, until disease progression. They consider three scenarios, where 30%, 50% or 100% of progression-free VEN+R patients receive ibrutinib treatment. Their analysis does not consider the possibility that patients with progressed disease may receive ibrutinib.

The ERG have summarised the results of the company in Table 1, and repeated the analysis with their preferred parametric modelling of survival. The ERG also explored scenarios where 10%, 30% or 50% of post progression patients would receive ibrutinib in addition to 50% of pre-progression patients. The ERG realises these may be pessimistic scenarios, as patients on the comparator arm are not receiving any treatment once they have progressed, however the results may still be of interest to the committee.

The ERG obtained marginally different cost estimates to the company for VEN+R when 30% of progression free patients were assumed to take ibrutinib, but otherwise found the company's analysis to be correctly performed. The comparison to the ERG preferred parametric curve show the results are not sensitive to choice of parametric curve. In the analyses presented below, which assume equal efficacy between VEN+R and ibrutinib, VEN+R appears to be the cheaper therapy.

Note that these analyses include the CAA on venetoclax, but do not include the discount on ibrutinib.

Treatment	Active treatment	Treatment admin	PFS health state costs	PPS health state costs	Terminal care costs	Treatment specific monitoring	AEs	Total
Company 100% of pre-progression on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company 50% of pre-progression on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company 30% of pre-progression on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Gen Gamma) 100% of pre-progression on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Gen Gamma) 50% of pre-progression on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG (Gen Gamma) 30% of pre-progression on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG alternative 50% of pre-progression and 10% post-progression patients on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG alternative 50% of pre-progression and 30% post-progression patients on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG alternative 50% of pre-progression and 50% post-progression patients on ibrutinib								
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VEN+R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 1: updated ERG preferred base–case model with waning effect applied to PFS and OS estimates for VEN+R in the comparison with ibrutinib (R/R CLL population). Weibull paramedic survival curves fitted and hazard ratios were estimated from the ERGs indirect comparison based on more recent data cut (May 2018) from MURANO

ERG exploration	Total costs VEN+R	Total LYs VEN+R	Total QALYs VEN+R	Total costs Ibrutinib	Total LYs Ibrutinib	Total QALYs Ibrutinib	Incremental costs	Incremental LYs	Incremental QALYs	ICER (LYs)	ICER (QALYs)
Updated Company's base case	[redacted]	9.679	6.356	[redacted]	6.252	4.349	[redacted]	3.426	2.007	[redacted]	[redacted]
Updated ERG preferred base-case model	[redacted]	9.679	6.356	[redacted]	10.171	6.717	[redacted]	-0.492	-0.361	[redacted]	[redacted]
Applied 10%	[redacted]	9.345	6.151	[redacted]	10.171	6.717	[redacted]	-0.826	-0.566	[redacted]	[redacted]
Applied 20%	[redacted]	9.043	5.966	[redacted]	10.171	6.717	[redacted]	-1.128	-0.751	[redacted]	[redacted]
Applied 50%	[redacted]	8.29	5.506	[redacted]	10.171	6.717	[redacted]	-1.88	-1.211	[redacted]	[redacted]
Applied 70%	[redacted]	7.887	5.259	[redacted]	10.171	6.717	[redacted]	-2.283	-1.458	[redacted]	[redacted]
Applied 100%	[redacted]	7.39	4.952	[redacted]	10.171	6.717	[redacted]	-2.781	-1.765	[redacted]	[redacted]
Applied 200%	[redacted]	6.295	4.272	[redacted]	10.171	6.717	[redacted]	-3.876	-2.445	[redacted]	[redacted]
[redacted]											
Updated Company's base case	[redacted]	9.679	6.356	[redacted]	6.252	4.349	-£160,506	3.426	2.007	-£46,845	Dominant
Updated ERG preferred base-case model	[redacted]	9.679	6.356	[redacted]	10.171	6.717	-£247,802	-0.492	-0.361	£503,461	£685,563
Applied 10%	[redacted]	9.345	6.151	[redacted]	10.171	6.717	-£248,672	-0.826	-0.566	£301,003	£439,419
Applied 20%	[redacted]	9.043	5.966	[redacted]	10.171	6.717	-£249,496	-1.128	-0.751	£221,171	£332,384
Applied 50%	[redacted]	8.29	5.506	[redacted]	10.171	6.717	-£251,685	-1.88	-1.211	£133,841	£207,797
Applied 70%	[redacted]	7.887	5.259	[redacted]	10.171	6.717	-£252,921	-2.283	-1.458	£110,766	£173,415
Applied 100%	[redacted]	7.39	4.952	[redacted]	10.171	6.717	-£254,495	-2.781	-1.765	£91,519	£144,205
Applied 200%	[redacted]	6.295	4.272	[redacted]	10.171	6.717	-£258,089	-3.876	-2.445	£66,594	£105,545

Table 2: updated ERG preferred base–case model with waning effect applied to PFS and OS estimates for VEN+R in the comparison with ibrutinib (R/R CLL population). Gamma paramedic survival curves fitted and hazard ratios were estimated from the ERGs indirect comparison based on more recent data cut (May 2018) from MURANO

ERG exploration	Total costs VEN+R	Total LYs VEN+R	Total QALYs VEN+R	Total costs IBRU	Total LYs IBRU	Total QALYs IBRU	Incremental costs	Incremental LYs	Incremental QALYs	ICER (LYs)	ICER (QALYs)
Updated Company's base case (Weibull parametric fits)	[redacted]	9.679	6.356	[redacted]	6.252	4.349	[redacted]	3.426	2.007	[redacted]	[redacted]

Updated ERG preferred base-case model	[redacted]	9.951	6.552	[redacted]	10.433	6.921	[redacted]	-0.482	-0.369	[redacted]	[redacted]
Applied 10%	[redacted]	9.345	6.151	[redacted]	10.171	6.717	[redacted]	-0.826	-0.566	[redacted]	[redacted]
Applied 20%	[redacted]	9.302	6.149	[redacted]	10.433	6.921	[redacted]	-1.13	-0.773	[redacted]	[redacted]
Applied 50%	[redacted]	8.524	5.666	[redacted]	10.433	6.921	[redacted]	-1.909	-1.255	[redacted]	[redacted]
Applied 70%	[redacted]	8.103	5.405	[redacted]	10.433	6.921	[redacted]	-2.33	-1.516	[redacted]	[redacted]
Applied 100%	[redacted]	7.578	5.08	[redacted]	10.433	6.921	[redacted]	-2.854	-1.841	[redacted]	[redacted]
Applied 200%	[redacted]	6.295	4.272	[redacted]	10.171	6.717	[redacted]	-3.876	-2.445	[redacted]	[redacted]
[redacted]											
Updated Company's base case (Weibull parametric fits)	[redacted]	9.679	6.356	[redacted]	6.252	4.349	-£160,506	3.426	2.007	-£46,845	Dominant
Updated ERG preferred base-case model	[redacted]	9.679	6.356	[redacted]	10.171	6.717	-£247,802	-0.492	-0.361	£503,461	£685,563
Applied 10%	[redacted]	9.951	6.552	[redacted]	10.433	6.921	-£274,822	-0.482	-0.369	£570,490	£744,429
Applied 20%	[redacted]	9.611	6.341	[redacted]	10.433	6.921	-£275,532	-0.821	-0.581	£335,447	£474,448
Applied 50%	[redacted]	9.302	6.149	[redacted]	10.433	6.921	-£276,231	-1.13	-0.773	£244,358	£357,457
Applied 70%	[redacted]	8.524	5.666	[redacted]	10.433	6.921	-£278,185	-1.909	-1.255	£145,747	£221,639
Applied 100%	[redacted]	8.103	5.405	[redacted]	10.433	6.921	-£279,341	-2.33	-1.516	£119,887	£184,251
Applied 200%	[redacted]	7.578	5.08	[redacted]	10.433	6.921	-£280,858	-2.854	-1.841	£98,401	£152,547

Table 3: updated ERG preferred base–case model with waning effect applied to PFS and OS estimates for VEN+R in the comparison with ibrutinib (R/R CLL population). Generalised Gamma paramedic survival curves fitted and hazard ratios were estimated from the ERGs indirect comparison based on more recent data cut (May 2018) from MURANO

ERG exploration	Total costs VEN+R	Total LYs VEN+R	Total QALYs VEN+R	Total costs IBRU	Total LYs IBRU	Total QALYs IBRU	Incremental costs	Incremental LYs	Incremental QALYs	ICER (LYs)	ICER (QALYs)
Updated Company's base case (Weibull parametric fits)	[redacted]	9.679	6.356	[redacted]	[redacted]	4.349	[redacted]	3.426	2.007	[redacted]	[redacted]
Updated ERG preferred base-case model	[redacted]	9.693	6.332	[redacted]	[redacted]	6.682	[redacted]	-0.494	-0.351	[redacted]	[redacted]
Applied 10%	[redacted]	9.369	6.136	[redacted]	[redacted]	6.682	[redacted]	-0.818	-0.546	[redacted]	[redacted]
Applied 20%	[redacted]	9.076	5.96	[redacted]	[redacted]	6.682	[redacted]	-1.111	-0.723	[redacted]	[redacted]
Applied 50%	[redacted]	8.348	5.519	[redacted]	[redacted]	6.682	[redacted]	-1.839	-1.163	[redacted]	[redacted]
Applied 70%	[redacted]	7.958	5.282	[redacted]	[redacted]	6.682	[redacted]	-2.229	-1.4	[redacted]	[redacted]

Applied 100%	[redacted]	7.476	4.988	[redacted]	[redacted]	6.682	[redacted]	-2.711	-1.694	[redacted]	[redacted]
Applied 200%	[redacted]	6.407	4.328	[redacted]	[redacted]	6.682	[redacted]	-3.78	-2.355	[redacted]	[redacted]
[redacted]											
Updated Company's base case (Weibull parametric fits)	[redacted]	9.679	6.356	[redacted]	[redacted]	4.349	-£160,506	3.426	2.007	-£46,845	Dominant
Updated ERG preferred base-case model	[redacted]	9.693	6.332	[redacted]	[redacted]	6.682	-£228,230	-0.494	-0.351	£462,066	£651,136
Applied 10%	[redacted]	9.369	6.136	[redacted]	[redacted]	6.682	-£229,206	-0.818	-0.546	£280,100	£419,799
Applied 20%	[redacted]	9.076	5.96	[redacted]	[redacted]	6.682	-£230,113	-1.111	-0.723	£207,118	£318,471
Applied 50%	[redacted]	8.348	5.519	[redacted]	[redacted]	6.682	-£232,459	-1.839	-1.163	£126,400	£199,876
Applied 70%	[redacted]	7.958	5.282	[redacted]	[redacted]	6.682	-£233,757	-2.229	-1.4	£104,880	£166,980
Applied 100%	[redacted]	7.476	4.988	[redacted]	[redacted]	6.682	-£235,394	-2.711	-1.694	£86,839	£138,934
Applied 200%	[redacted]	6.407	4.328	[redacted]	[redacted]	6.682	-£239,111	-3.78	-2.355	£63,251	£101,550