NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of TA491)

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Review

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The **final scope and final stakeholder list** are available on the NICE website.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA491

Waldenstrom's macroglobulinaemia - ibrutinib [ID3778]

Company evidence submission for committee

July 2021

File name	Version	Contains confidential information	Date
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Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

If applicable provide any supportive and detailed methodological or investigative evidence (additional to the clinical trial and/or Systemic Anti-Cancer Therapy data) in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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A.1 Background

Waldenström's macroglobulinaemia (WM) is a rare, debilitating, and incurable form of non-Hodgkin's lymphoma (NHL), which accounts for <1% of all cancer diagnoses in England.(1) Ibrutinib received marketing authorisation from the European Medicines Agency (EMA) for the treatment of patients with WM in 2015. (2) Ibrutinib is the first and currently the only licensed treatment that specifically targets the disease itself. Marketing authorisation was granted based on the results of Study 1118E, a phase 2 single-arm investigator-initiated study (IIS) of 63 patients in the US. Despite the limited evidence base, reflecting the rarity of the disease, the EMA deemed it to be appropriate to demonstrate the clinical benefit of ibrutinib in this population.

In 2017, NICE recommended ibrutinib for the treatment of patients with WM within the NHS in England via the new Cancer Drug Fund (CDF).(3) The Terms of Engagement (ToE) document states that "*Ibrutinib is recommended for use in the CDF as an option for treating WM in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement (MAA) for ibrutinib are followed*".(4) As per the MAA, data has been collected over a three year period from the publication of the MAA in September 2017. The timeframe for data collected to be compiled into the final Public Health England (PHE) report (allowing for trusts to upload their data, and PHE to develop a report containing systemic anti-cancer therapy (SACT) data) added 8 months to the MAA period. This combined with the timelines for NICE CDF review means that [redacted] within the CDF for four years.

Importantly, 823 patients have benefited from ibrutinib within the CDF,(1) which is more than double the 335 patients originally expected,(5) demonstrating how significant the unmet need was and still is in this population. This emphasises the importance of ibrutinib being available within NHS routine commissioning once this period of managed access ends, otherwise management of patients with WM will be once again limited to off-label drugs that can only alleviate symptoms.(6)

The Committee has acknowledged ibrutinib is a "*step change in managing WM*"(7) recognising that there is a the lack of tolerable and effective treatment options for these patients in England. Additionally, expert insights gathered from clinicians and patients throughout the course of the NICE appraisal supported ibrutinib's unprecedented effectiveness, its well tolerated safety profile and its significant improvement in patients' quality of life (QoL). Furthermore, the convenience of this oral therapy further benefits patient's QoL and alleviates resource use within the NHS, the value of which has only been amplified by the COVID-19 pandemic. A patient expert who had been on treatment with ibrutinib for several years explained it was a "*life-transforming*" drug that "*dramatically*" improved their QoL, allowing them to return to normal life, including work.

The original NICE submission in 2016(8) was built around progression-free survival (PFS) from 63 patients treated with ibrutinib monotherapy in Study 1118E (after 24 months of follow-up).(9) Whilst data from 31 patients treated with ibrutinib monotherapy within an ongoing sub-study (called iNNOVATE Arm C) were presented alongside Study 1118E, median follow-up was only 7.7 months and these patients were more heavily pre-treated with poorer prognosis, meaning they were not representative of the indicated population. At time of the original submission, there were no UK-specific WM real-world data as the national WM Rory Morrison Registry (RMR) was still under construction. In the absence of any comparative data for ibrutinib vs standard of care from trials or observational studies, the relative clinical benefit of ibrutinib was derived through an indirect treatment comparison (ITC) leveraging data from a "European Chart Review" in patients treated for WM.

The Committee's decision to recommend ibrutinib for use within the CDF was driven by uncertainty in the clinical evidence base, as discussed in the Final Appraisal Determination (FAD). It is important to note, however, that some uncertainties (such as that associated with long-term extrapolations) are inherent to an orphan and indolent disease and therefore challenging to resolve.(7) The Data Collection Arrangement (DCA) that underpins the MAA states that data were to be collected across four data sources to address the key areas of uncertainty flagged in the FAD; these included the SACT database, Study 1118E, iNNOVATE arm C and the RMR.

Janssen has built its new company base-case around the 3-year data from SACT,(1) which the DCA defined as the primary data source for this CDF review. Given SACT does not report data on PFS, which is pivotal for the economic modelling, Janssen has also leveraged data from the UK-based RMR (Appendix B.2.2) to help address this data gap. A scenario analysis has been conducted in which modelled PFS is derived using the 5 years of data from Study 1118E.(10) Updated results from iNNOVATE Arm C(11) are presented in this CDF review; however, given limitations in representativeness of these patients, these data are supportive evidence only and not used in the updated economic model.

Despite new evidence collected across multiple data sources over the past four years, some residual areas of uncertainty remain around key clinical inputs, namely:

Ibrutinib PFS benefit in clinical practice (SACT): while the SACT dataset can be deemed the data source most representative of English clinical practice, SACT does not collect data on PFS. The DCA suggested that treatment duration (TD) could be used as a proxy for progression, however over the course of the data collection period, it has become apparent that TD is not a reasonable proxy for PFS. SACT data in combination with BlueTeq data, plus evidence from Study 1118E 5-year data-cut suggests that the relationship between TD and PFS is not equal. Indeed, SACT data(1) shows that 67% of patients had stopped treatment but had not progressed or died. In Study 1118E, median TD had been reached while median PFS still had not been after 5-years of follow-up. Discontinuation of treatment ahead of progression is thought to be due to the accumulation of toxicities or patient choice.(10) Hence Janssen has implemented an approach to modelling PFS in its new company base-case that is based on the assumption that TD is shorter than PFS (see Section 9). In the absence of SACT PFS data, two scenarios were conducted to explore the impact of different approaches to modelling SACT PFS (see Section A.12.2).

Ibrutinib relative clinical benefit: since no standard of care existed in WM, a mixed treatment basket reflecting existing off-label treatment options (named “Physician’s Choice” [PC]) was accepted as an appropriate comparator by the Committee (see Section A.2). In the absence of any comparative data, the relative clinical benefit for ibrutinib versus PC was derived using an ITC based on patient-level data (PLD) from Study 1118E and a “European Chart Review” in WM.(12) This was a large

observational retrospective study (n=454) commissioned by Pharmacyclics that generated data on epidemiology, treatment and efficacy outcomes (including PFS) for patients with treatment-naïve and relapsed WM over 10 years. Whilst the ToE document highlighted the uncertainty in relative effectiveness of ibrutinib, further updates or improvements in the ITC are not feasible with the available evidence (see Section A.7). Since the ITC approach was broadly accepted by the Committee, this analysis has been maintained in the new company base-case.

PPM in ibrutinib arm: PPM refers to death that occurs prior to a patient progressing as a result of the disease, hence PPM can be defined as a “composite” outcome that includes data on both mortality and progression. The estimate for PPM in the FAD was based on the number of deaths that occurred pre-progression as observed in Study 1118E and derived by the ERG. Given SACT does not collect data on progression, new evidence from SACT cannot resolve uncertainty in this outcome, so the FAD PPM estimate has been maintained in the new company base-case (see Section A.6.3). A scenario analysis was conducted using on-treatment mortality data from SACT, as a proxy for PPM and a further analysis used PPM data from the RMR (see Section A.12.2). Janssen acknowledges that the remaining uncertainty reflects the challenge to reliably collect these data outside of a trial setting.

Long-term OS: WM is known to be an indolent form of NHL, with a median OS spanning 4 to 12 years.(13) This means it is not clinically plausible to fully resolve concerns around the maturity of survival data within the timeframe of an MAA, since such uncertainty is inherent to the disease setting. Median OS has not been reached in any of the four data sources in scope for this review, confirming both the indolent nature of WM and the significant survival benefit of ibrutinib.

In summary, Janssen has strived to make the best use of the new clinical evidence according to the DCA(5); however some residual uncertainties inherent to an orphan and indolent disease remain. Recommendation of ibrutinib for baseline commissioning within the NHS is imperative to fulfil the ongoing clinical need for an efficacious and tolerable treatment option for patients with WM in England.

A.2 Key committee assumptions

Table 1. Key Committee assumptions

Assumption subject	Committee preferred assumptions	Adherence or departing form assumption	Justification (if needed)
Population	Adults with WM who have had at least 1 prior therapy are the relevant population for the CDF review.	Adhering to assumption	NA
Comparators	The company should present clinical and cost-effective evidence for ibrutinib compared to the "PC" comparator that was used for decision-making within the original appraisal.	Adhering to assumption	NA
Survival data	The company should use more mature, PFS and OS data using data collected through SACT, Study 1118E, iNNOVATE and the WMUK registry.	Adhering to assumption	• New data from the RMR and more mature evidence from Study 1118E will be incorporated to inform modelled PFS, whilst TD data from SACT will be used to inform modelled TD (since TD is not deemed an accurate proxy for PFS). • New or mature OS data from the various evidence sources will not be used directly in the model given the model utilises a Markov approach whereby OS is a composite outcome calculated as "OS = 1-overall mortality", where overall mortality is estimated as the summation of death from the initial PFS treatment phase (upon patients entering the model) and the post-progression phases (1st subsequent treatment, 2nd subsequent treatment and best supportive care) (see updated model schematic in Appendix B.1.6). • Data from iNNOVATE Arm C will be presented as supportive evidence as the small cohort of 31 patients in iNNOVATE Arm C were refractory to rituximab and more heavily pre-treated than those in Study 1118E (see Appendix B.3).
Pre-progression mortality	The company should use data collected through SACT, and more mature data from	Adhering to assumption	<u>Reminder on modelling approach for OS</u> • As explained above, overall mortality was estimated as the summation of death from the initial PFS treatment phase and

	Study 1118E and iNNOVATE to inform pre-progression mortality. Time to progression rather than time to subsequent treatment should be used to calculate pre-progression mortality.		the post-progression phases. The death rates in each disease phase are estimated based on the phase-specific probability of death. Death from the initial PFS treatment phase (upon patient entry in model) is based on a probability of death during this phase/health state – this input is that referred to as "pre-progression mortality" (PPM) below. Different assumptions were used in the FAD model for ibrutinib and the comparator arm. <u>Ibrutinib PPM:</u> • Since Study 1118E is an IIS, Janssen does not have access to PPM PLD beyond the 24m data-cut. As such the PPM rate estimated in the FAD (as per ERG Scenario #3), which was based on the 3 deaths occurring pre-progression in the 24m data-cut, will be retained in the new company base-case. • Whilst SACT does not capture data on disease progression, SACT can provide an estimate for on-treatment mortality, considered a proxy for PPM. Acknowledging limitations in accurately capturing TD in the real-world, these data will be used in a scenario analysis to test the impact on the new company base-case. • Data from iNNOVATE Arm C will be presented as supportive evidence as per rationale above. <u>PC PPM:</u> • PC PPM will be modelled according to the Committee's preferred approach (i.e. discarding deaths that had occurred between progression and next treatment) as adopted in the FAD model (see Appendix B.11). Hence no update will be made to these data in the new company base-case.
Comparative effectiveness	The company should fully explore the most appropriate comparison based on data collected during the period of managed access, with particular focus on whether data from iNNOVATE can be used to establish the relative effectiveness of ibrutinib compared to standard of care.	Departing from assumption	• As explained above, patients in iNNOVATE Arm C (n=31) represent a small cohort of patients who are refractory to rituximab and more heavily pre-treated than those in Study

			1118E and SACT. As a result, these patients have a poorer prognosis. • Updating the ITC with these data is also not feasible because once adjustments are made for differences in key patient characteristics and prognostic factors, the effective sample size would be too small to enable any meaningful analysis. Analyses would likely be associated with very wide confidence intervals and thus unnecessarily introduce even greater uncertainty. • Since no further exploration around comparative effectiveness is feasible, and the Committee deemed the ITC approach suitable at time of FAD, no further update to this analysis has been carried out.
Most plausible ICER	Committee concluded that there was uncertainty about the size of the clinical benefit and the modelling of pre-progression mortality and that the most plausible ICER is likely to be at least £54,100 per QALY gained. Committee did not think this estimate was cost-effective but heard from the company that they had made an offer to provide ibrutinib at a price that resulted in ibrutinib being cost-effective within the CDF.	Adhering to assumption	• Ibrutinib is available to all NHS patients treated within baseline commissioning through a simple discount patient access scheme of [redacted]. This existing discount will apply to the indication covered by this submission.
End of life	Ibrutinib does not meet the end-of-life criteria.	Adhering to assumption	NA
BSC: best supportive care; CDF: Cancer Drug Fund; ERG: Evidence review group; FAD: Final appraisal determination; ICER: incremental cost-effectiveness ratio; NHS: National Health System; OS: overall survival; PFS: progression-free survival; PPM: progression-free survival; QALY: quality-adjusted life years; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy; TD: treatment duration.			

A.3 Other agreed changes

As reflected in Section A.2 above, Janssen has not made any significant change to the decision problem described in the ToE document;(4) no additional evidence has been presented beyond the agreed data which has been collected to address the key uncertainties in scope for CDF Review of TA491, and described in the DCA.

The same model has been used in this CDF review as in the original appraisal (model version dated 10Nov2016, shared in response to the ACD). To optimise the use of available data across model parameters, some updates have been made to improve the accuracy and functionality of the model.

Of note, these changes are clearly outlined both in Appendix B.1 and in the model interface, and the FAD ICER can be easily replicated. The impact these updates have on the new company base-case can also be explored easily within the model functionality.

A.4 The technology

Table 2. Technology being reviewed: ibrutinib

UK approved name and brand name	**Ibrutinib (Imbruvica®).**
Mechanism of action	Ibrutinib is a potent, orally bioavailable, highly specific inhibitor of Bruton Tyrosine Kinase (BTK).(14-16) Sustained inhibition of BTK activation and function is accomplished when ibrutinib binds to a critical cysteine residue (Cys-481), forming a stable, covalent bond and blocking entry to the adenosine triphosphate (ATP) binding domain of BTK.
Marketing authorisation/CE mark status	On the 3rd of July 2015, ibrutinib as a single agent was granted marketing authorisation by the European Commission (EC) for the treatment of adult patients with WM: • who have received at least one prior therapy (previously treated) or • frontline whom are ineligible for chemo-immunotherapy.
Indications and any restriction(s) as described in the summary of product characteristics	Ibrutinib is indicated for the treatment of adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Ibrutinib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. The use of preparations containing St. John's Wort is contraindicated in patients treated with ibrutinib. Ibrutinib (Imbruvica®) is also indicated:(2)

	• As a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy; • As a single agent for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL); • As a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). • In combination with obinutuzumab or rituximab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
Method of administration and dosage	• Dosage is 420 mg once daily (od) • Ibrutinib is administered as an oral monotherapy and is taken until disease progression or until the treatment is no longer tolerated by the patient.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	Ibrutinib is available at a list price of £51.10 per 140mg tablet.(17) Ibrutinib is taken until disease progression or until the treatment is no longer tolerated by the patient. The cost per year of treatment is £55,954.50, estimated based on list price and dosing regimen. Median treatment duration with ibrutinib is 24.9 months as per SACT 3-year report (see Section A.6.1)
Commercial arrangement (if applicable)	Currently a simple discount patient access scheme (PAS) is in place for all ibrutinib indications funding via baseline commissioning. This existing discount of [redacted] will apply to the indication covered by this submission. [redacted]
Date technology was recommended for use in the CDF	September, 2017
Data collection end date	September, 2020

A.5 Clinical effectiveness evidence

As per the DCA, SACT (see Table 3 below) is the primary data source of clinical evidence for this CDF review. The SACT database has collected data on 823 patients with WM from Trusts in England and is therefore deemed the source most generalisable to NHS clinical practice.

SACT however does not collect data on disease progression, which informs two key outcomes highlighted as areas of uncertainty in the FAD: PFS and PPM. Whilst SACT provides data for on-treatment mortality as a proxy for PPM, and treatment duration as a proxy for progression, there are key limitations in this approach.

Table 3. Primary source of clinical effectiveness evidence - SACT

Study title	**SACT data cohort study (3-year final analyses)(1)**
Study design	SACT real-world data cohort study*
Population	WM patients with at least one prior line of treatment, receiving ibrutinib based on Blueteq criteria (N=823)
Intervention(s)	Ibrutinib
Comparator(s)	Not applicable
Outcomes collected that address committee's key uncertainties**	On-treatment mortality **Treatment duration** **Overall survival**
* SACT data is supplemented by Blueteq data presented in the PHE SACT 3-year report. **Data for outcomes marked in bold are used in company's new base-case.	

Given the inherent limitations of robust data collection within orphan diseases, especially in the real-world setting, no single source of evidence can comprehensively provide sufficient data to address the key uncertainties presented in the ToE.(4) As a result, it is important to recognise and focus on where uncertainty is resolvable, and it is necessary to leverage data from multiple sources in order to best address the decision problem.

As such, the new company base-case (see Sections A.8 and A.9) primarily leverages SACT data, where appropriate, alongside data from additional "supportive" sources outlined in the DCA (see Table 4 below).

Table 4. Secondary sources of clinical effectiveness evidence

Study title (acronym)	PCYC-1118E(10)	PCYC-1127-CA (iNNOVATE)(11)	Rory Morrison Registry
Study design	Phase 2 trial	Phase 3 RCT with open-label sub-study (arm C)	Retrospective observational study
Clinicaltrial.gov ref.	NCT01614821	NCT02165397	NA
Data-cuts CCOD and median follow-up in months (m)	The initial NICE submission was based on results from median 14.8m (primary analyses)(18) and 24m (update 1) follow-up analyses, with an update at 37m (update 2).(19) Below are further data-cuts: • Update 3 – CCOD NR (47.1m)(20) • Update 4 – CCOD NR (50m)(21) • Final analyses – CCOD NR (59m)(10)	In the initial NICE submission results from median 7.7m follow-up analyses were presented for arm C,(22) with an update at 17.1m.(23) Below are key further data-cuts: • Primary analyses - CCOD NR (18.1m)(24) • First CSR – CCOD October 2017 (34.4m)(25) • Final analyses & CSR – CCOD December 2019 (57.9m)(11)	Analyses – CCOD April 2020 (median follow-up: [redacted])
Population Key eligibility criteria	WM patients with at least one prior line of therapy Inclusion: • Age ≥18 years. • Measurable disease, defined as the presence of serum IgM with a minimum IgM level >2 times the institutional ULN) • Clinicopathological diagnosis of WM. • Necessity of treatment based on IWWM guidelines. • At least 1 prior therapy for WM. • ECOG performance status of ≤2.	Arm C: WM patients who relapsed within 12 months of last rituximab-containing treatment or who failed to respond to rituximab-containing therapy and not eligible for randomisation Inclusion: • Patients with centrally confirmed diagnosis of WM and symptomatic disease requiring treatment per 2nd International Workshop on WM criteria. • Disease refractory to the last rituximab-containing therapy defined as either relapse after <12	WM patients with at least one prior line of therapy Inclusion: • Age ≥ 18 years old • Ibrutinib monotherapy as ≥ 2nd line of therapy Exclusion: • Other therapies than ibrutinib as ≥ 2nd line for RR WM • Ibrutinib as a combination • Prior use of ibrutinib

	• Adequate hematologic, renal, and hepatic function. • No active therapy for other malignancies with the exception of topical therapy for basal cell or squamous cell skin cancers. <u>Exclusion</u>: • Warfarin anticoagulation therapy. • Diagnosed lymphoma of the central nervous system.	months or failure to achieve at least a minor response. • Haemoglobin ≥8 g/dL. • Platelet count >50,000 cells/mm3 (50 x 109/L). • Absolute neutrophil count >750 cells/mm3 (0.75 x 109/L). • Serum aspartate transaminase or alanine transaminase <3.0 x ULN. • Bilirubin ≤1.5 x ULN. • IgM ≥ 0.5 g/dL. <u>Exclusion:</u> • Central nervous system involvement. • Clinically significant cardiovascular disease. • Previous therapy for WM ≤30 days prior to first treatment dose.	
Intervention(s)	Ibrutinib (monotherapy) (n=63)	Ibrutinib (monotherapy) (n=31)	Ibrutinib (monotherapy) (n=112)
Comparator(s)	NA	NA	NA
Outcomes collected that address committee's key uncertainties*	• Treatment duration • Progression-free survival • Overall survival	• Treatment duration • Progression-free survival • Overall survival • Pre-progression mortality	• **Treatment duration** • **Progression-free survival** • Overall survival • On-treatment mortality • Pre-progression mortality
Data governance	PCYC-1118E (referred to as "Study 1118E" subsequently in this submission) is the pivotal registrational study. Study 1118E is an IIS; beyond the 24-month data-cut, Janssen do not have access to any PLD. The 59-	PCYC-1127 (referred to as "iNNOVATE" subsequently in this submission) is a study sponsored by Pharmacyclics in collaboration with Janssen. Arm C is the non-	The RMR was established in August 2017 to capture real world evidence for patients with WM. The RMR captures a wide range of patient data relating to demographics, clinical features, treatments, molecular

	month data-cut (i.e. final analysis) for this submission is only available as aggregated data presented at ICML 2019 congress(26) and also published in Treon *et al.* 2020.(10)	randomised arm (sub-study) of the Phase 3 RCT.	genetics and other laboratory parameters, progression of disease and patient reported outcomes. At the time of the retrospective study, data was collected from 15 centres across England and 1 centre in Wales.
Reference to section in appendix	None	None	B.2
CCOD: Clinical cut-off dates; CSR: clinical study report; ECOG: Eastern Cooperative Oncology Group; ICML: International Conference on Malignant Lymphoma; IgM: Immunoglobulin; IIS: investigator-initiated study; IWWM: International Workshop on WM; NA: not applicable; NR: not reported; PCYC: Pharmacyclics; RCT: randomised controlled trial; RMR: Rory Morrison Registry; RR: relapsed/refractor; ULN: upper limit of normal; WM: Waldenström's macroglobulinaemia *Data for outcomes marked in bold are used in company's new base-case.			

A.6 Key results of the data collection

This section presents results of the new and updated evidence collected across all four data sources specified in the DCA(5) and in the ToE document.(4) It also highlights which of these data feeds specifically into the new company base-case. The detail of how these data are incorporated into the model is subsequently presented in Sections A.7 -A.9 . Given the differences in underlying patient baseline characteristics (see Appendix B.3) and in patients' geographic origin across the four data sources, cross-source comparison of results for each outcome should be interpreted with caution.

A.6.1 *Treatment duration*

TD has been included in the DCA for two reasons: i) as a proxy for PFS in SACT (see Section A.8.2 below) and ii) to derive on-treatment mortality as a proxy for PPM in SACT (see Section A.8.3 below). In the real-world setting, capturing treatment end date for an oral therapy such as ibrutinib is a significant challenge because it is taken at home and therefore clinicians would typically capture end of treatment using the date from the last prescription as a guide. This means there are inherent limitations in the TD data from SACT and the RMR. Table 5 below presents evidence gathered on TD across the four data sources during the data collection period.

Table 5. TD updated data and new evidence

Data source	Comment
1118E (N=63)	After a median follow-up of 59 months (final analyses), **median TD was 46 months**,(26) reported as a single data-point with no further detail or KM data provided .
SACT (N=823)	After a median follow-up of 12.9 months (SACT 3-year final analyses), **median TD was 24.9 months** (95% CI: 21.8-28.9).(1) This estimate was derived using PHE methodology on calculating TD for oral drugs, which suggests that ibrutinib TD estimate was based on the last recorded treatment date (cycle/administration) + 28 days prescription length.(27-29)
RMR (N=112)	After a median follow-up of [redacted]*, **median TD was** [redacted] (see Appendix B.2.2). TD was recorded retrospectively by clinicians upon a patient completing treatment and thus this estimate should also be treated with caution.
iNNOVATE, Arm C (N=31)	After a median follow-up of 57.9 months (final analyses), **median TD was 40.7 months** ([redacted]).(11, 30)

CDF: Cancer Drug Fund; CI: confidence interval; NR: not reached; PHE: Public Health England; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy; TD: treatment duration *median follow-up period following commencement of ibrutinib.

Conclusion on TD: Error! Reference source not found. below presents a visual overlay of TD from the evidence sources available. Variation in reported TD across data sources may be attributed to differing length of follow-up and/or differences in key patient characteristics, such as age and number of lines of prior therapy. For example, older age is typically associated with shorter TD, and the shortest TD is reported for the SACT population (median age: 75 years) which is on average 5 and 12 years older than the RMR and Study 1118E cohorts, respectively.

Figure 1. Available data for TD [SACT, RMR, Study 1118E, iNNOVATE Arm C]

1118E: Study 1118E; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy

As noted above, there are significant issues in accurately capturing the end of treatment for oral therapies in the real word setting and hence there are also differences in the way TD is reported between data sources, making naive comparability a challenge. Acknowledging, however, that the SACT database is the primary source of new evidence in this CDF review, data on TD from SACT was used to inform ibrutinib treatment costs and leveraged to derive modelled PFS in the new company base-case.

A.6.2 *Progression-free survival*

PFS is pivotal for informing the length of time a patient remains at the same disease stage, before experiencing disease progression and associated decrements to quality of life. At the time of initial submission, the only source for ibrutinib PFS was Study 1118E, yet median PFS had still not been reached after 37-months of follow-up, hence this outcome was deemed an area of uncertainty in the FAD. Where possible, additional and/or updated evidence gathered during the data collection period are presented herein in Table 6 to support the significant PFS benefit of ibrutinib.

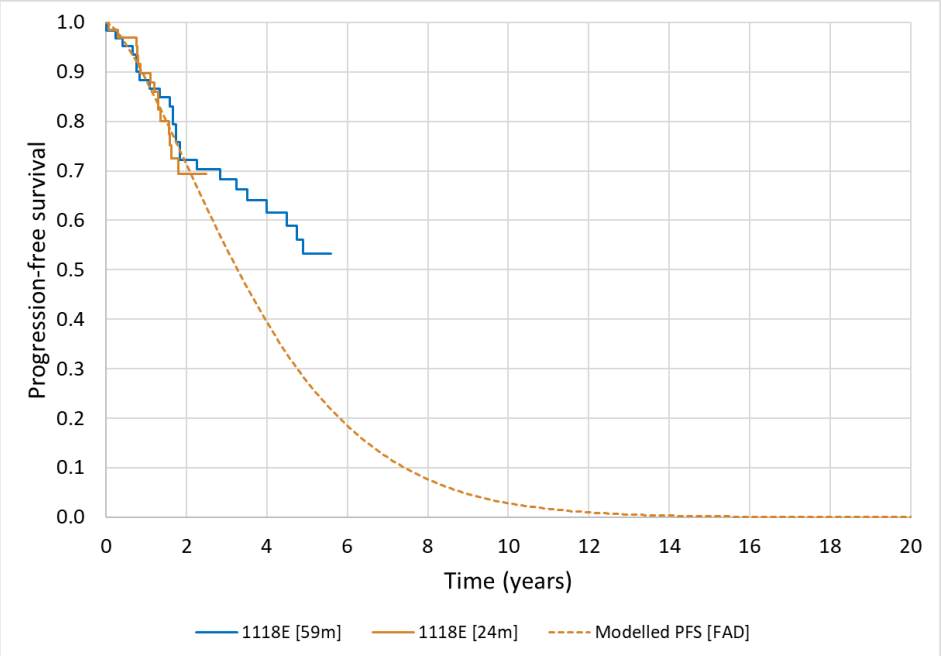
Table 6. PFS updated data and new evidence

Data source	Comment
1118E (N=63)	After a median follow-up of 59 months (final analyses), **median PFS had still not been reached** and the **5-year PFS rate was 54%** (95%CI: 39.0-67.0).(10)
SACT (N=823)	**PFS was not collected by SACT** because disease progression is not an endpoint captured within the standard dataset. Whilst the DCA suggests that TD collected by the SACT database could be used as a proxy for progression,(5) 67% of SACT patients have stopped treatment but have not progressed(1) showing that the relationship between TD and PFS is not equal. Evidence from Study 1118E final data-cut(10) further substantiates this since, after 5 years, median TD has been reached but median PFS has still not been reached.
RMR (N=112)	After a median follow-up of [redacted]*, **median PFS was** [redacted] (Appendix B.2.2).
iNNOVATE, Arm C (N=31)	After median follow-up of 57.9 months (final analyses), **median PFS** (measured by IRC) **was 38.7 months** (95%CI: 25.0-NE) and the **5-year PFS rate was 39.7%** ([redacted]).(11, 30) The fact median PFS has been reached in iNNOVATE arm C but not in Study 1118E over a similar median follow-up period (57.9 vs 59 months) is likely due to patients in Arm C being refractory to rituximab - hence a population likely to have a poorer prognosis (Appendix B.3)
CI: confidence interval; DCA: Data collection agreement; FAD: Final appraisal determination; IRC: Independent review committee; NE: not estimable; PFS: progression-free survival; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy; TD: treatment duration. *median follow-up period following commencement of ibrutinib.	

Notably, Figure 2 below shows how PFS projections within the original NICE submission (after 24 months of follow-up) were clearly conservative and underestimated since the 5-year PFS rate from Study 1118E final analysis (after 59

months of follow-up) now has now demonstrated a 5-year PFS rate of 54%, superior to a previously estimated 27%.

Figure 2. Study 1118E modelled PFS curve in FAD base-case vs 59m KM curve



1118E: Study 1118E; FAD: final determination appraisal; PFS: progression-free survival

Conclusion on PFS: Figure 3 below shows a visual overlay of the KM data from the evidence sources now available for PFS. Acknowledging the differences in patient characteristics and extent of pre-treatment between study cohorts (Appendix B.3), it is also relevant to highlight that variances in PFS may also reflect differences in definition and/or reporting of progression between clinical practice and trials (Appendix B.4).

Figure 3. KM data for PFS [RMR, Study 1118E, iNNOVATE Arm C]

1118E: Study 1118E; IRC: Independent review committee; RMR: Rory Morrison Registry

In the absence of PFS data from SACT, and limitations in using TD as a proxy for progression, modelled PFS in the new company base-case was derived using available RMR evidence. Since the RMR cohort (n=112) captures patients with WM treated within the NHS, it may be considered a subset of the SACT dataset (n=823) (see Appendix B.2). RMR PFS was adjusted using SACT TD (see Section A.8.2). In order to also leverage the long-term evidence from Study 1118E, a scenario analysis was also conducted in which PFS was derived from trial data (see Section A.12.2).

A.6.3 *Pre-progression mortality*

PPM refers to death that occurs prior to a patient progressing as a result of the disease. Hence PPM can be defined as a "composite" outcome that includes data both on mortality and progression. At the time of initial NICE submission, Study 1118E reported 3 deaths in total,(9) all of which had occurred prior to progression although these data were relatively immature since median follow-up was only 24 months.(10) In the FAD model, the estimate for PPM is a rate (λ=0.0019) derived by the ERG (exploratory analysis #3) based on a 1-year probability which was itself estimated based on these 3 deaths, the number of patients and the mean time of

patient exposure.(31) Table 7 below presents evidence gathered on PPM across the four data sources during the data collection period.

Table 7. PPM updated data and new evidence

Data source	Comment
1118E (N=63)	At median follow-up of 59 months (final analyses), **no further data** on PPM had been published beyond that presented for the 24-month follow-up in Treon *et al.* 2015.(9) Since 1118E is an IIS, Janssen do not have access to the PLD of the final analysis.
SACT (N=823)	Since SACT did not collect data on progression, on-treatment mortality derived from data on TD was deemed a proxy for PPM - in the DCA, PPM is defined as "*the number of death events and time to death that occur while on treatment*".(5) Overall, **6% (53/823)** of all SACT patients died while on treatment with ibrutinib. Median survival was not reached.(1)
RMR (N=112)	After a median follow-up of [redacted],* [redacted] of all patients had died on treatment (Appendix B.2.2) – in line with SACT estimate above. The RMR also collected data on the number of patients who died prior to progressing, which amounts to a proportion of [redacted] and [redacted] (Appendix B.2.2).
iNNOVATE, Arm C (N=31)	After median follow-up of 57.9 months (final analyses), a total of [redacted] had occurred, [redacted] of which [redacted] prior to progression hence the proportion of patients who died pre-progression is [redacted].(11)

CI: confidence interval; DCA: Data collection agreement; IIS: investigator-initiated study; PLD: patient level data; PPM: pre-progression mortality; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy; TD: treatment duration.
*median follow-up period following commencement of ibrutinib.

Conclusion on PPM: Data for PPM across the four sources are heterogeneous because these data have not been consistently reported within each trial/dataset (i.e. PPM versus on-treatment morality), and even when the number of deaths has been reported, there has not always been clarity on which deaths have occurred pre- vs post progression. Variation in underlying patient baseline characteristics (see Appendix B.3), the length of follow-up, and differences in how/when progression was defined or how/when mortality was captured, are all contributing factors.

Given the challenges capturing PPM in the real world and the fact that more mature PPM data is not available from 1118E, the new company base-case maintained the PPM rate derived by the ERG in the original submission (i.e. exploratory analysis #3 from the ERG report)(31). Nevertheless, two scenario analyses have been

conducted, using SACT on-treatment mortality and RMR PPM respectively, to explore impact of this parameter on cost-effectiveness.

A.6.4 *Overall Survival*

The DCA highlights overall survival as an area of uncertainty and thus an outcome in scope for data collection. Median OS however has still not been reached in any data source presented herein as shown in Table 8. This is not unexpected since WM is an indolent disease and median life expectancy spans 4-12 years in the literature.(13) Nevertheless, an additional 3 years of OS data reduces the uncertainty in long-term survival extrapolations and the fact that median OS has not been reached is very positive for patients given they are living even longer with ibrutinib treatment.

Table 8. OS updated data and new evidence

Data source	Comment
1118E (N=63)	After median follow-up of 59 months (final analyses) **median OS had not been reached** and **87% of patients were still alive after 5 years** (95%CI not reported).(10) Note: at 24m, **95%** (95% CI: 86%-98%) of patients were alive.(9)
SACT (N=823)	After median follow-up of 19 months (SACT 3-year final analyses), median OS has not been reached and **61% of patients** (95% CI: 56%-65%) were still alive at **3 years**.(1) Note: at 24m, **73%** (95% CI: 69%-76%) of patients were alive.(1)
RMR (N=112)	After median follow-up of [redacted],* median OS has not been reached and [redacted] were still alive at **30 months** (Appendix B.2.2). Note: at 24m, [redacted] of patients were alive (Appendix B.2.2).
iNNOVATE, Arm C (N=31)	After a median follow-up of 57.9 months, **median OS had not been reached** and [redacted] were still alive after **5 years** ([redacted]).(11) Note: at 24m, [redacted] of patients were alive.(11)
OS: overall survival; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy; TD: treatment duration. *median follow-up period following commencement of ibrutinib.	

Conclusion on OS: Figure 4**Error! Reference source not found.** shows a visual overlay of the KM data available for OS. At 24 months, the proportion of patients alive was 95% and [redacted] in Study 1118E and iNNOVATE arm C respectively, versus [redacted] and 73% in the RMR and SACT datasets respectively. Observed OS data show that real-world sources are associated with lower OS rates than trial sources and this

is likely due to the differences in underlying patient baseline characteristics; for example, younger cohorts are evidentially going to live longer than the older cohorts. Indeed this holds true when naively comparing data from the RMR with that from SACT.

Figure 4. KM data for OS [SACT, RMR, Study 1118E, iNNOVATE arm C]

1118E: Study 1118E; RMR: Rory Morrison Registry; SACT: systemic anti-cancer therapy

To leverage NHS data where appropriate, OS data from SACT was used in the new company base-case (see Section 8 below). Of note, while SACT is generalisable to NHS practice, it is likely that the most severe patients have been initiated on treatment within the CDF first, meaning the new company base-case may be a conversative estimate of survival.

A.7 Evidence synthesis

Study 1118E is a single arm study that assesses the efficacy and safety of ibrutinib for the treatment of RR WM. In the absence of a single standard of care at the time of the initial NICE submission, the relevant comparator was defined as “PC” (see Section A.2 above). Therefore, to estimate relative efficacy of ibrutinib vs. PC in terms of PFS, an ITC was required.

At the time of original submission, to derive relative PFS benefit Janssen used PLD from Study 1118E 24-month follow-up and PLD from a study referred to as the

“European Chart Review” (ECR). This was a retrospective observational study (n=454) of patients with symptomatic WM that started treatment which generated data on epidemiology, treatment and efficacy outcomes for treatment-naïve and relapsed WM patients over 10 years.(12)

Given the differences in patient characteristics across the two studies, populations were matched, using a re-sampling methodology, based on number of prior lines of treatment as this is a prognostic factor for PFS. A total of 175 patients from the ECR PC cohort were included in the ITC. Multivariate cox regression analyses were then conducted to estimate ibrutinib PFS benefit compared to PC adjusting for remaining differences in patient characteristics, yielding a hazard ratio (HR) of [redacted] for PFS.

While the Committee acknowledged the data limitations to estimate the relative PFS benefit of ibrutinib vs PC, it overall accepted the ITC used by Janssen to derive the PFS HR.(7)

Since no comparative efficacy data can be collected through SACT, there is limited new evidence to address uncertainty in the ITC, and the analysis cannot be updated or improved with the use of other data sources either. Indeed, the uncertainty in the ITC cannot be reduced with longer follow-up data from Study 1118E because, given this is an IIS, no further PLD are available. Using aggregated evidence from the published 59m data-cut would therefore only incorporate greater uncertainty into the analysis. Uncertainty in the ITC also cannot be reduced using iNNOVATE because there were only 31 patients in Arm C, all of whom were refractory to rituximab and more heavily pre-treated with poorer prognosis than those in Study 1118E and SACT. As such, once adjustments are made for differences in patient characteristics and prognostic factors, the effective sample size would be too small to enable any meaningful analysis. Analyses would likely be associated with very wide confidence intervals and thus unnecessarily introduce even greater uncertainty into the modelling.

In summary, no additional comparative efficacy data was collected by the sources in scope of the CDF review and no updated trial data could be used to further resolve uncertainty in the analysis. As such, no further exploration around comparative

effectiveness was feasible. The HR of [redacted] from the FAD base-case is therefore maintained within the new company base-case.

A.8 Incorporating collected data into the model

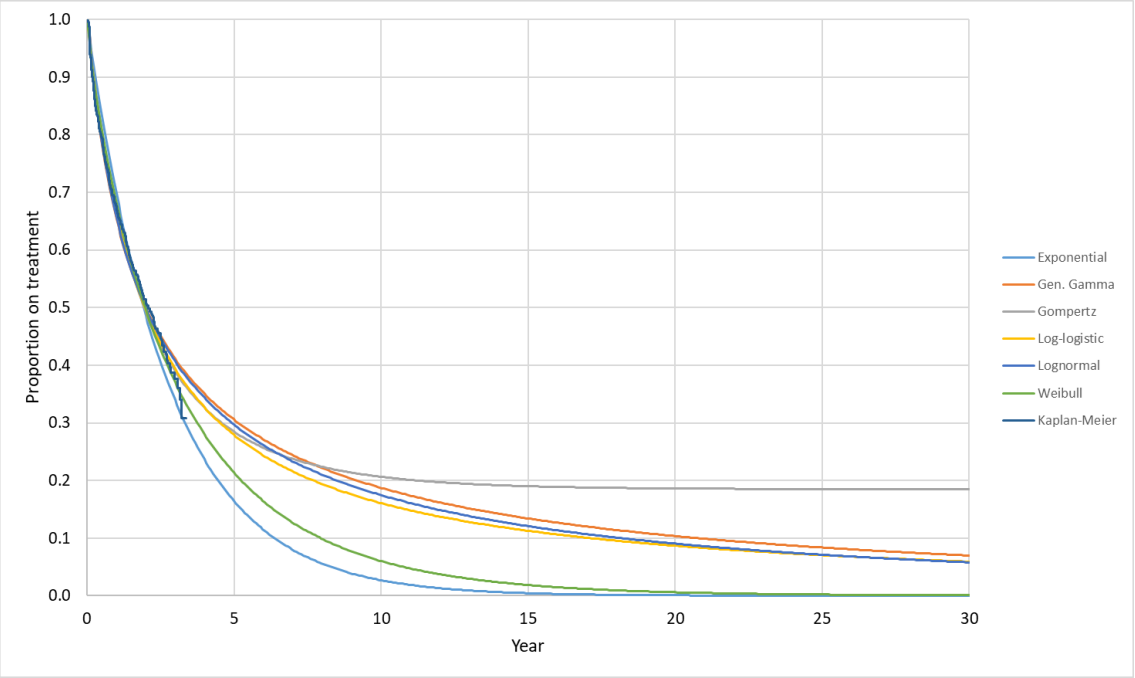
This section focuses on specific data presented in Section A.6 which is utilised in the new company base-case. The detail of the changes to the model that result from the incorporation of new evidence can be found in Appendix B.1.

A.8.1 *Treatment duration*

TD from the final SACT report was used to derive TD in the new company base-case.(1) The number of patients at risk, the number that were censored and the number that ended treatment (events) from the time they started treatment to the end of the follow-up (FU) period are presented in Appendix B.5. Of the 823 patients who received treatment, 455 were still on treatment at the date of follow-up and 368 had completed treatment. Median TD for ibrutinib was 24.9 months.

The SACT KM plot for TD [SACT report, page 20, Figure 3] was digitised, and parametric curves were fitted using the method described in Appendix B.5. The exponential distribution shown in Figure 5 below was chosen to inform the base-case analysis as the long-term projections were deemed to be closest to expected TD in clinical practice. Full methods and justification are provided in Appendix B.5.

Figure 5. Kaplan–Meier curve and extrapolations for TD (SACT report)



Gen. Gamma: generalized gamma; SACT: Systemic Anti-Cancer Therapy; TD: treatment duration.

A.8.2 *Progression-free survival*

As PFS was not collected in the SACT dataset, for the new company base-case, it was necessary to derive PFS using alternative data sources. RMR data was considered as the RMR cohort represents a subset of the SACT population and the registry was the only relevant evidence source available that reported both PFS and TD KM data in a single study. Median PFS was [redacted] (Appendix B.2.2).

The KM plot for ibrutinib PFS presented from the RMR analyses (Appendix B.2.2) was digitised and parametric curves fitted using the method described in Appendix B.5. The exponential distribution was chosen to inform the base-case analysis as this was the best statistically fitting curve (as reported in Appendix B.5) and was consistent with the approaches used to extrapolate TD and OS KM data in Sections A.8.1 and A.8.4 respectively. Full methods and justification are provided in Appendix B.5.

Predicted ibrutinib PFS in SACT was derived by adjusting parametric curves fitted to the observed RMR PFS based on the relationship between SACT TD and RMR TD. The relationship was based on the restricted mean survival in both datasets for the maximum SACT treatment duration of follow-up (1.92 years)(1) using KM data [SACT report, page 20, maximum follow-up 1,156 days] (see Table 9).

Table 9. Hazard ratio: SACT TD versus RMR TD for maximum SACT follow-up

Domain	Value
Maximum follow-up in SACT	1,156 days (~3.165 years)
Restricted mean survival for TD in RMR	[redacted]
Restricted mean survival for TD in SACT	1.92 years
Estimated hazard ratio for SACT TD vs RMR TD	[redacted]
RMR: Rory Morrison Registry; SACT: Systemic Anti-Cancer Therapy; TD: treatment duration.	

SACT maximum follow-up was used because it was the maximum time point for which data were available from both datasets. In addition, small numbers at risk for RMR treatment duration (n=2) were noted beyond this time point.

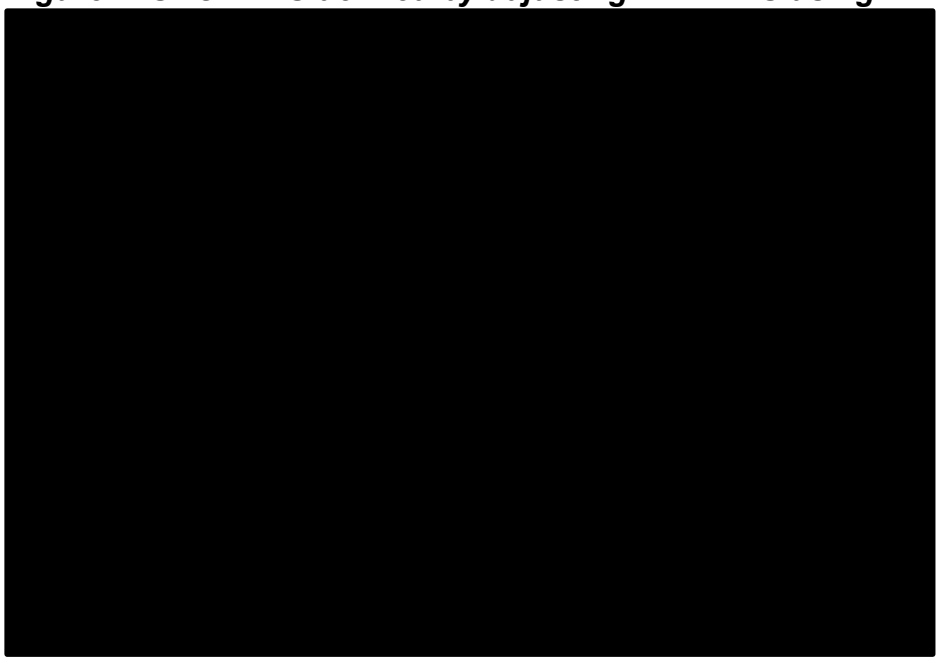
A plot of all six down-weighted parametric curves derived is shown in Figure 6. The exponential and Weibull curves remained the most conservative extrapolations, with the exponential selected for the base-case to align with the unadjusted RMR PFS approach.

Figure 6. SACT PFS using RMR extrapolations adjusted with TD hazard

Gen. Gamma: generalized gamma; KM: Kaplan-Meier; PFS: progression-free survival; RMR Rory Morrison Registry.

Figure 7 shows the derived SACT PFS extrapolation compared to SACT TD and RMR PFS.(1)

Figure 7. SACT PFS derived by adjusting RMR PFS using TD hazard



KM: Kaplan–Meier; PFS: progression-free survival; RMR: Rory Morrison Registry; SACT: Systemic Anti-Cancer Therapy; TD: treatment duration.

The resulting curve was validated by clinician insights. A scenario was conducted in which the length of follow-up used to calculate the hazard adjustment for treatment duration was reduced to 24 months, matching the time point at which the numbers at risk in SACT or RMR remained reasonably high (i.e. did not reduce below 10%).(32) At 2 years, the numbers at risk were 194 out of 823 in SACT (23.6%) and [redacted] in RMR ([redacted]). Details of the data and calculations to derive the hazard can be found in Appendix B.6. A further scenario analysis was run to test the impact on the ICER of following the same approach to derive PFS as in the base-case but using a different dataset, Study 1118E (see Appendix B.7).

A.8.3 *Pre-progression mortality*

As explained and justified in Section A.6.3 , the PPM rate estimated in the FAD (as per exploratory analysis #3 in ERG report(31)), which was based on the three deaths occurring pre-progression in the 24-month data-cut, was retained in the new company base-case. Of note, at time of original submission, the ERG expressed concern related to how PPM was implemented where the observed death rate in 1118E was lower than sex-adjusted general population mortality until patients were 74 years or older (ERG Report page 115, Section (5)).(31) This approach was

addressed in the FAD model where PPM was calculated based on number of death events, the number of patients and the mean number of patient years exposure.

Given how pivotal PPM is to the CDF review, two scenario analyses were conducted in which SACT on-treatment mortality and RMR PPM was used respectively to contextualise the FAD PPM rate; details of the data and approach to deriving the PPM model estimates for these scenarios can be found in Appendix B.8 and B.9.

A.8.4 *Overall survival*

The SACT report(1) reported the minimum follow-up (FU) as 6 months (182 days) from the last CDF application to the date patients were traced for their vital status.(1) Patients were traced for their vital status on 29 March 2021; this date was used as the follow-up date (censored date) if a patient was still alive and the median follow-up time (from the start of their treatment to death or censored date) was 19.0 months (578 days).

The KM plot for OS for ibrutinib indicated that median survival was not reached. The plot was converted to a digitised image and parametric curves fitted using the method described in Appendix B.5. The exponential distribution was chosen for the base-case analysis, as this was the best statistically fitting curve (Appendix B.5), which was also validated by clinicians. Full methods and justification are provided in Appendix B.5.

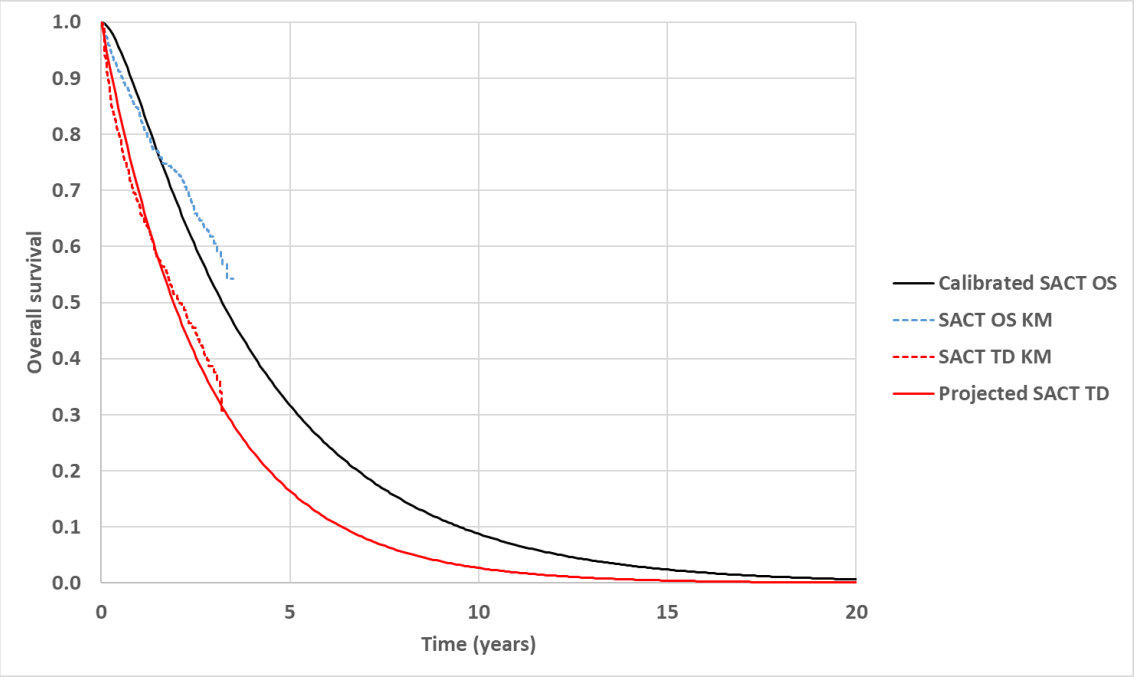
OS using SACT was incorporated into the model by calibrating post-progression survival using the data from the final report. The following steps were taken:

- The number of patients progressed was calculated as the difference between SACT [derived] PFS using RMR data and SACT OS. The number of patients who died in pre-progression was calculated from SACT [derived] PFS using PPM for ibrutinib from Study 1118E. The cumulative number of patients who died in post-progression was calculated as the difference between total death (1 – OS) and pre-progression mortality. The cumulative number of patients who died post-progression was expressed as a proportion of total deaths (1 – OS) to derive a survival function for post-progression over time. This survival function was used to estimate mean post-progression survival.

- To calibrate the model OS to align with SACT OS KM, a calibration factor was calculated by dividing the original modelled post progression survival for the maximum follow-up in SACT (1278 days) by the restricted mean survival from SACT over the same follow up time. The resulting multiplier was then used to increase the probability of post-progression mortality from the European Chart Review (i.e. [redacted] per model cycle).

The resulting projected OS aligned reasonably well with the SACT OS KM, given the assumptions needing to be made for mortality (constant hazards) shown in Figure 8.

Figure 8. Comparison of calibrated model OS and SACT KM and projected OS



KM Kaplan-Meier; OS: overall survival; SACT: Systemic Anti-Cancer Therapy study; TD: treatment duration.

A.9 Key model assumptions and inputs

As reported in Section A.6 above, the sources in the scope for this review provide data of varying breadth and granularity. Given the heterogeneity of the new evidence, no single source could comprehensively provide sufficient data to address all key data points and associated uncertainties presented in the ToE document.(4) Therefore, assumptions had to be made around the comparability of datasets to optimise the use of the available evidence in the most appropriate way.

While the new company base-case was primarily based on SACT data(1) to ensure that outcomes are most representative of English clinical practice for the treatment of WM, data from the RMR and Study 1118E were also leveraged where necessary. A summary of key model assumptions and inputs is presented in Table 10 below.

The new evidence available for this CDF review suggests, as would be expected given the summary of product characteristics (treatment until progression or unacceptable toxicity), that TD is shorter than PFS. TD was therefore modelled independently in all analyses to accurately account for costs incurred by patients treated with ibrutinib. In the new company base-case, modelled TD was informed by SACT data. Since the SACT dataset does not collect data on progression, PFS and PPM model inputs were derived from alternative data sources. PFS was derived using data from RMR (considered a subset of SACT), with a scenario based on data from Study 1118E. The PPM estimate from the FAD model (derived by the ERG in exploratory analysis #3 from ERG report),(31) was retained for the company base-case, with two scenario analyses conducted using SACT on-treatment mortality and RMR PPM respectively.

Long-term OS from Study 1118E (after 59 months of follow-up) indicated higher survival rates compared to those observed in SACT (Figure 4). SACT data was therefore used to calibrate the post-progression survival used in the original FAD model, still assuming equal post-progression survival for both arms.

In the absence of SACT comparative data, and given that no further PLD were available from the Study 1118E, the relative PFS benefit derived from the ITC in the original submission and broadly accepted by Committee, was retained in the new company base-case.

Table 10. Key model assumptions and inputs (new company base-case)

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Patient age	Study 1118E mean age [64.5 years] from patient baseline characteristics	SACT median age [75 years] from patient baseline characteristics(1)	SACT patient age was used as base-case analysis intends to model outcomes for a cohort that is generalisable to the English RR WM population. In the absence of any mean reported in the SACT final report,

			median age was used – this is a limitation from the SACT dataset.
Ibrutinib PFS [A.8.2 B.5.2 (page 47)]	Evidence from 24m FU from Study 1118 (patient level data) CCOD = 12/12/2014(9)	PFS derived from RMR [redacted] FU data CCOD = 04/2020 (Appendix B.2.2)	No PFS evidence available from SACT; PFS was derived from RMR data as the RMR cohort is a subset of the SACT population. Assumptions made to derive SACT PFS were validated by clinicians.
HR PFS for ibrutinib vs Physician's Choice [A.7	Evidence from 24m FU from Study 1118(9) & ECR (ITC).	No update	No comparative evidence available from SACT and no comparative data from Study 1118E, a Phase II single-arm study. The initial ITC was based on PLD. Unfortunately, only aggregate PFS data are available from Study 1118E for the 59m data-cut given that it is an IIS.
Ibrutinib TD [A.8.2 B.5.1 (page 45)]	Parameter not included in FAD base case	TD from 3Y SACT data CCOD = 27/09/2020(1)	TD for ibrutinib was included as a stand-alone model input to accurately account for costs incurred by patients treated with ibrutinib.
Ibrutinib PPM [A.8.3	PPM derived from 24m FU from Study 1118E(9)	No update	Given that SACT only collects on-treatment mortality, PPM use in FAD base case was retained.
Ibrutinib OS [A.8.4 B.5.3 (page 49)]	Constant hazard of death post-progression from ECR fourth treatment line	Uses constant hazard of death in FAD, adjusted using post-progression survival hazard to calibrate modelled OS to SACT KM from 3-year report CCOD = 27/09/2020(1)	Median OS in SACT was not reached. Adjustment to post-progression mortality hazard retained the FAD model structure and calibrated OS to match SACT OS KM.

CCOD: clinical cut-off dates; ECR, European Chart Review; FAD, final appraisal documentation; FU, follow-up; HR, hazard ratio; IIS: investigator-initiated study; ITC: Indirect treatment comparison; NR: not reported; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PLD, patient-level data; PPM, pre-progression mortality; RMR: Rory Morrison Registry; SACT, Systemic Anti-Cancer Therapy study; TD, treatment duration.

A.10 Cost-effectiveness results (deterministic)

Table 11 presents two base-cases as required by the ToE document. Firstly, the FAD base-case from the original submission (generated by model version dated 10Nov2016 shared in response to the ACD). The ICER of £54,141/QALY gained is based on

[redacted].

Secondly, the new company base-case from this CDF review, accounting for new evidence collected during this period of managed access and updated modelling. The ICER of [redacted] is also based on [redacted].

Of note, [redacted].

Table 11. Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
FAD base-case							
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician's choice	[redacted]	[redacted]	[redacted]	-	-	-	-
New company base-case							
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician's choice	[redacted]	[redacted]	[redacted]	-	-	-	-
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life years							

Of note, it is not feasible to conduct an analysis which incorporates new evidence gathered through the data collection process whilst simultaneously maintaining all prior modelling assumptions because some model adjustments were mandatory in order to accommodate the format of the new data (e.g. a new input was created for TD, that previously was not modelled in the FAD base-case, see Appendix B.1). Therefore, no such scenario is presented in Table 11.

A.11 Probabilistic sensitivity analysis

To assess the uncertainty around the model inputs included in the base-case cost-effectiveness analysis, a probabilistic sensitivity analysis (PSA) was conducted using 1,000 iterations. Of note, the PSA has been enhanced in the CDF model compared to the FAD model to improve the accuracy of results and simultaneously address some concerns the ERG had raised in the ERG report. The updated methodology, including the specific distribution of all parameters is presented in Appendix B.1.5.

Table 12 below presents the ICER generated for the new company base-case using the PSA and shows that results are very similar to the deterministic analyses.

Table 12. Probabilistic base-case results (PAS price) – B.1.5 (page 19)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician's choice	[redacted]	[redacted]	[redacted]	-	-	-	-
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life years							

Error! Reference source not found. presents the scatter plot of probabilistic results for ibrutinib compared to PC, which shows the incremental costs and QALYs for each iteration.

Figure 9. Scatterplot of probabilistic results (PAS price) – B.1.5 (page 19)

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

A.12 Key sensitivity and scenario analyses

A.12.1 *One-way sensitivity analysis*

The tornado diagram presented in Figure 10 shows the impact on the ICER when individually varying model parameters. The tornado diagram shows that, out of the 15 parameters, four have a significant impact on the ICER: the PFS HR for ibrutinib vs PC (ibrutinib relative clinical benefit), the HR used to derive ibrutinib SACT PFS based on RMR data (new input in CDF model) and the discounts applied to health

outcomes and costs respectively. Of note, varying ibrutinib PPM was no longer found to be a key driver of the ICER in this CDF review and therefore does not appear within the tornado diagram. Further detail on the approach to updating the OWSA is provided in Appendix B.1.4.

Figure 10. Tornado diagram (PAS price) – B.1.4 (page 12)

HR, hazard ratio; PC, physician's choice; PFS, progression-free survival; PP, post-progression; PPS, post-progression survival; RMR, Rory Morrison Registry; SACT, Systemic Anti-Cancer Therapy; TD, treatment duration.

The detail of OWSA results is presented in Table 13 below. The ICERs ranged from [redacted] to [redacted] for ibrutinib vs PC, compared to [redacted] in the new company base-case.

Table 13. One-way sensitivity analyses results (PAS price)

#	Parameter	Lower bound ICER (£/QALY)	Upper bound ICER (£/QALY)
1	HR PFS ibrutinib vs PC	[redacted]	[redacted]
2	HR SACT vs RMR PFS	[redacted]	[redacted]
3	Discount health	[redacted]	[redacted]
4	Discount cost	[redacted]	[redacted]
5	Dose intensity	[redacted]	[redacted]

6	Utility PFS	[redacted]	[redacted]
7	IV administration cost	[redacted]	[redacted]
8	FU costs - All treatments - year 3 - 5	[redacted]	[redacted]
9	Terminal Care cost	[redacted]	[redacted]
10	FU costs - All treatments - year 1-2	[redacted]	[redacted]
11	Probability of death during SubTx1 Ibr	[redacted]	[redacted]
12	SACT PPS hazard adjustment	[redacted]	[redacted]
13	FU costs - All treatments - year 6+	[redacted]	[redacted]
14	Time horizon	[redacted]	[redacted]
15	Probability of death during BSC Ibr	[redacted]	[redacted]
ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme.			

A.12.2 *Scenario analyses*

Six scenario analyses were conducted to test outstanding uncertainty around key assumptions made in the new company base-case. Scenarios 1-5 were based on the new company base-case (see Section A.9) which is anchored to SACT data:

- Scenario 1 was conducted to test the impact of using the Weibull distribution as opposed to the exponential distribution in the base-case to extrapolate SACT TD as TD is a key model input which impacts SACT-derived PFS and ibrutinib total costs.

- Scenario 2 & 3 were conducted to test the impact on the base-case ICER of estimating SACT PFS, a key cost-effectiveness driver, using a different modelling approach and a different dataset respectively.

- Scenarios 4 & 5 were explored to leverage PPM derived from the real-world setting, i.e. SACT and the RMR respectively. Whilst PPM was stated as a key area of uncertainty in the FAD, it is no longer a key driver of the ICER in this CDF review (see Section A.12.1 above).

Scenario 6 was anchored to trial data (instead of SACT), with TD, PFS and PPM data all taken from Study 1118E. This is to test the impact of using updated long-term trial data as opposed to real world evidence in the new company base-case.

For all scenarios, as for new company base-case analysis, costs and life table data were updated and modelling corrections were implemented (see Appendix B.1.2 and

B.1.3). An overview of the scenarios is presented in Table 14 below; additional modelling information is provided in the Appendix sections referenced in the table.

Table 14. Key scenario analyses

Scenario and cross reference	Scenario detail	Modelling information in Appendix	Brief rationale	Impact on base-case ICER
New company base-case				[redacted]
Scenarios based on SACT data				
[1] Ibrutinib SACT TD	Weibull distribution used instead of exponential distribution	None	Weibull distribution was used as an alternative to exponential distribution used in base-case as the Weibull distribution represents the middle option within the range of distributions considered as clinically plausible.	[redacted]
[2] Ibrutinib RMR-derived PFS [alternative approach]	Alternative HR was generated to adjust RMR PFS based on a time period for which 10 to 20% of patients from SACT and RMR remain in either TD KM.	Appendix B.6	In base-case, RMR-derived PFS is based on a HR for the difference in treatment duration between SACT TD and RMR TD using area under the curve; it uses the maximum follow-up from SACT, which is 3.17 years. Scenario explores calculating the HR using data over a time period for which 10 to 20% of patients remain in either KM. This approach is based on the uncertainties in interpretation of KM data once numbers at risk fall below 10 to 20%.(32)	[redacted]
[3] Ibrutinib trial-derived PFS	PFS based on Study 1118E 59m data-cut(10) instead of RMR data	Appendix B.7	Assumption for ibrutinib PFS is a key model driver; in the absence of SACT PFS data, an alternative PFS was derived from Study 1118E as an alternative to RMR used in the base-case.	[redacted]
[4] Ibrutinib SACT on-treatment mortality	PPM was derived from SACT on-treatment mortality(1) instead of Study 1118E	Appendix B.8	PPM from FAD, which was based on Study 1118 data, was used in base-case; given no PPM data was collected from SACT, impact of using SACT on-treatment mortality, used as proxy for PPM, was also tested.	[redacted]
[5] Ibrutinib RMR PPM	PPM was derived from the RMR dataset (Appendix B.2.2) instead of Study 1118E	Appendix B.9	Additional scenario testing the impact of using an alternative PPM value – this PPM estimate is derived from RMR cohort deemed a subset of SACT and also used to model PFS.	[redacted]
Scenario based on Study 1118E data				

[6] Ibrutinib Study 1118E inputs	Ibrutinib TD & PFS were taken from trial 59m data-cut(22); patient mean age same as in FAD	Appendix B.10	Key model drivers were informed with data from Study 1118E to explore a scenario based on long-term data from a more homogeneous dataset.	[redacted]
ICER: incremental cost-effectiveness ratio; HR: Hazard Ratio; KM: Kaplan-Meier; PFS: progression-free survival; PPM: pre-progression mortality; PPS: post-progression survival; RMR: Rory Morrison Registry; SACT: Systemic Anti-Cancer Therapy; TD: treatment duration				

A.13 Key issues and conclusions based on the data collected during the CDF review period

WM is a rare disease with high unmet need: ibrutinib is the only licensed treatment for patients with WM that specifically targets the disease. A total of 823 patients have benefited from ibrutinib within the CDF during the data collection period.(1) This is more than double than the 335 patients originally expected.(5) Ibrutinib quickly became standard of care for patients in the relapsed/refractory setting, which highlights how significant the patient and clinical need is in this population. Without ongoing access to ibrutinib, disease management would revert to using ineffective, off-label therapies which can only attempt to alleviate symptoms.(6)

Ibrutinib offers significant value to the NHSE and to patients: in 2017, ibrutinib was recommended by NICE for use within the CDF based on a commercial agreement providing ibrutinib to the NHS [redacted]. This recommendation was for all patients with WM who have already been treated with one prior line of therapy, while further evidence is collected to address the uncertainty around key clinical assumptions. While the data collection period set out in the DCA was three years, the time between the publication of the FAD (09/2017) and the conclusion of this re-appraisal will be over four years. As such, [redacted] to more than double the number of patients originally expected but has also been provided for a significantly longer period than initially planned, which has afforded NHS England significant savings over the managed access period. Finally, ibrutinib is an oral therapy taken in the comfort of a patient's home, thereby avoiding hospital visits and associated resource use and relieving NHS capacity. This is of utmost value to the NHS and patients, which has only been amplified through the COVID-19 pandemic.

Residual uncertainty in the decision problem is inherent to the disease and the datasets: some of the key areas of uncertainty stated in the FAD(7) and the ToE document(4) are inherent to any rare and indolent disease, such as WM, and cannot be resolved beyond the new evidence gathered for this CDF review. For example:

- Median OS has not been reached with any of the data sources, even with Study 1118E final analysis, after 5-years of follow up. Whilst this is hugely positive for

patients and not unexpected, given median OS reported in the literature is typically between 4-12 years, it does mean that residual uncertainty in long-term extrapolations is unavoidable at time of this CDF review.(13)

- Study 1118E is an IIS therefore Janssen did not have access to PLD beyond the 24-month data-cut. In orphan diseases such as WM, it is not uncommon to see an IIS used both as a registrational trial and a pivotal data source in a NICE submission; hence limited data for endpoints such as PPM is due to the nature of the clinical research in rare diseases.

- There are limitations in the data collected and updated as part of the managed access period. Firstly, none of the datasets are able to provide robust comparative data to enable standard cost-effectiveness analysis. Phase 2 non-comparative studies are increasingly used as registrational trials for transformational cancer medicines in rare disease and SACT is not designed to capture comparative data as part of managed access. It can be expected that would SACT have had the potential to record comparative data, limited comparator data would have been collected for this CDF review, especially in second-line treatment, where ibrutinib is being used very broadly. Secondly, data collected within SACT are on a limited number of outcomes that do not necessarily match the pivotal outcomes used in the economic modelling and in scope for this CDF review, such as disease progression.

In summary, updated evidence from clinical trials and new evidence collected from real-world data sources cannot comprehensively fulfil all data-gaps and fully resolve the uncertainty in the evidence inherent to an orphan, indolent disease. However, the updated modelling has optimised use of evidence that is available to ensure the new company base-case is representative of English clinical practice to support this CDF review.

The clinical evidence base in orphan diseases is often heterogenous: evidence was gathered from four different sources, both investigational and non-investigational, and each one provided data with varying breadth and granularity. Consequentially, the collective evidence base available for this CDF review is heterogeneous in nature. As a result, no single source of evidence could

comprehensively provide sufficient data to address the key uncertainties presented in the ToE document,(4) and assumptions had to be made to use data from several sources in combination, both in the base-case and in the scenario analyses.

The new company base-case makes best use of available data: Janssen has made best use of the data gathered across the four sources in scope for the extended data collection period, to address Committee concerns discussed in 2016. The new company base-case was anchored to real-world evidence from SACT, as the primary data source in the DCA, with necessary supportive evidence from the RMR, which can be considered a subset of the SACT cohort. Specifically, in the absence of SACT data on progression, modelled PFS was derived leveraging data from the RMR. Given no new or updated evidence was available to enable further updates to initial estimates for comparative clinical benefit of ibrutinib vs PC, the original ITC has been retained in the new company base-case since this was broadly accepted by the Committee. The new company base-case ICER is [redacted], when accounting for [redacted]. Janssen has engaged with NHSE in parallel to this CDF review to explore mechanisms for providing ibrutinib to WM patients at a cost-effective price.

Comprehensive sensitivity analyses mitigate risk of uncertainty: six scenario analyses were conducted to explore the impact of adopting alternative assumptions and data sources on the ICER. The ICERs generated for these analyses range between [redacted] and [redacted], suggesting the new company base-case of [redacted] is within the range of clinically plausible estimates for cost-effectiveness.

Conclusion: the ICERs presented in this CDF review of TA491, based on new evidence from two real-world data sources representative of NHS clinical practice, and updated 5-year follow-up from Study 1118E, have optimised use of available evidence and addressed key areas of uncertainty highlighted in the FAD and ToE document. Collectively, all clinical data show the substantial benefit that ibrutinib offers to patients with WM and to the NHS, in terms of high survival rates, limited toxicities, oral administration and a step-change in quality of life. While the CDF has proved a useful mechanism to grant access to novel therapies where clinical benefit

is deemed uncertain at the time of an evaluation, inherent limitations for orphan and indolent diseases still pose hurdles for re-evaluation. Janssen is mindful that the new NICE methods will be published early next year and that these methods may provide an improved decision-making framework to accelerate access to innovative medicines for rare diseases. In the meantime, Jansen would like to highlight the benefits of ibrutinib that cannot be captured in the QALY framework; this includes the wider benefit of oral medicine on NHS resources which importance is amplified as the NHS recovers from a global pandemic, the benefits to carers and society of a “life-transforming’ innovation, as well as the value of research and innovation in rare diseases to improve equity across health conditions.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA491

Ibrutinib for Waldenstrom's macroglobulinemia (ID3778)

Clarification questions

July 2021

File name	Version	Contains confidential information	Date
ID3778 Ibrutinib WM CDF Clarification Questions to PM for company_ Janssen response _28Jul2021_REDACTED	1.0	No	28 July 2021

Section A: Clarification on effectiveness data

Indirect treatment comparison

A1. PRIORITY: Company submission (CS), Section A.7, page 25. Please comment on why the indirect treatment comparison was not updated, for example, using data from the European Chart Review and either the Rory Morrison Registry or the later data-cut of Study 1118E within a matching-adjusted indirect comparison.

The indirect treatment comparison (ITC) used in the FAD base-case (BC) to derive the relative progression-free survival (PFS) benefit of ibrutinib vs standard of care (SoC) was retained in the CDF Review new company BC as no further evidence was gathered on the relative PFS benefit of ibrutinib vs SoC during the CDF data collection period. While updated and new ibrutinib PFS data were collected as part of the 59-month Study 1118E data-cut and the Rory Morrison Registry (RMR) analyses respectively, only aggregate data were available from each source which means updating the ITC would have been associated with some technical challenges and/or limitations.

Firstly, leveraging the 59-month FU of 1118E would require an 'unanchored' MAIC. While technically this methodology is feasible, it is associated with more limitations than the original ITC and therefore would introduce greater uncertainty compared to the patient-level comparison conducted using European Chart Review (ECR) data vs the earlier trial data-cut.

Secondly, we recognise the interest in leveraging the RMR PFS data to inform relative benefit; however only aggregate data were available, meaning that comparison would require an unanchored MAIC. Additionally, variation in covariate data would likely impact effective sample sizes.

Finally, and as discussed with NICE and the ERG on 26 July 2021, there are significant limitations in conducting a MAIC to derive relative PFS benefit of ibrutinib vs SoC using SACT data since SACT did not collect data on disease progression. This means any MAIC would not only be unanchored, with limited covariates available for adjustment but it would also be comparing two different outcomes (i.e. PFS from ECR and treatment duration (TD) from SACT) which is not methodologically sound or appropriate where more suitable data exists.

Should the ERG find it helpful to see a comparison of covariate data across sources, Janssen is willing to follow up; however, this was not feasible within the given timeframe.

Section B: Clarification on cost-effectiveness data

Decision problem and data sources

B1. With the exception of pre-progression mortality (PPM) data and the derived hazard ratio (HR) for progression free survival (PFS), the updated CDF model does not use clinical effectiveness data from Study 1118E. Please comment on the extent to which the updated model reduces decision uncertainty compared with the original final appraisal determination (FAD) model.

As explained in the CS, Janssen has built their new company BC around the 3-year data from the systemic anti-cancer therapy (SACT) dataset, which the Data Collection Arrangement (DCA) defined as the primary data source for this CDF review. By following this approach Janssen ensured that the evidence used in the updated CDF model is more representative of English clinical practice, given the SACT patients are treated in the NHS in England. However, given that SACT does not collect data for progression as an endpoint, data from other sources had to be leveraged to provide data for PFS and PPM. Janssen acknowledged the limitations of this approach in the CS, explaining that leveraging a combination of data sources was essential since no single source provided sufficient information to address all parameters. Adopting such assumptions within the modelling was necessary given the nature of the heterogeneous evidence base, which is an inherent limitation in rare diseases, such as WM. As such, Janssen believes the new company BC does reduce uncertainty within the limitations posed by the new evidence that has been generated within the timeframe of the CDF data collection period.

Janssen further acknowledges the specificity of this CDF review: while the FAD BC was developed around study 1118E population (as no real-world evidence was available at the time of the initial submission), the new company BC is anchored to the SACT cohort. Nevertheless, Janssen would like to highlight scenario #6 which does provide an updated cost-effectiveness analysis leveraging updated 1118E data. Indeed, this scenario was anchored to the trial data (similar to the FAD BC),

with TD, PFS and PPM data all taken from Study 1118E. Specifically, TD and PFS were updated with evidence from the trial later (59-month) data-cut. As explained in the CS, no PPM data was available from Study 1118E beyond the 24-month data-cut, as this is an investigator-initiated study and no PPM was published for the later data-cut. This scenario enables to test the impact of updating the FAD BC with long-term trial data as opposed to real world evidence in the new company BC, further reducing the uncertainty flagged in the FAD.

B2. CS, Section A.6, page 18. Please provide information on the completeness of the data for treatment discontinuation (TD) and overall survival (OS) in SACT.

SACT TD and OS data presented in the CS are taken from the SACT 3-year report developed by Public Health England (PHE) in line with the DCA that stated SACT was the primary data collection for the CDF Review.

The SACT dataset does not include a field to collect data specifically for these two endpoints; instead, as explained in the SACT report, TD (p11-12) and OS (p13) were estimated by PHE based on data on: start date of regimen & cycle (SACT data item #22 & #27), administration date (SACT data item #34), and the outcome summary field, detailing the reason for stopping treatment has been completed (SACT v2.0 data item #41 and SACT v3.0 data item #58 - #61).

For data on completeness, Janssen would refer to Table 1 and Table 2, both on p15 in the SACT report. Table 1 presents the completeness of key data items for the broad CDF ibrutinib cohort (n=823) and reports a completion rate of 100% for start date of regimen & cycle as well as for administration date. Table 2 presents the completeness of regimen outcome summary for the subgroup of patients that have ended treatment (n=368) and reports a 70% rate for the outcome summary of why treatment was stopped.

Of note, both Janssen and the ERG are privy to the same extent of information from the SACT dataset, including that around completeness of the data, all of which is presented within the SACT 3-year report.

B3. CS Appendices, Section B.1.2, page 5. The table represents the updated drug acquisition costs to be used in the model. However, it seems the model ('Cost Inputs' sheet

cells D35:M42) is still using the same costs from the FAD model. Please comment and amend if necessary.

Janssen response no longer needed following discussion with NICE/ERG on 26 July 2021.

Extrapolation of time to event data

B4. PRIORITY. CS, Section A.8, pages 27-32. For each of the new survival analyses detailed in the CDF-CS, please explain how clinical input was used to judge the plausibility of parametric survival models. Did you: (a) ask the clinical experts for expectations of survival at multiple timepoints for patients treated with ibrutinib; (b) show the clinical experts the fitted parametric survival predictions, or (c) ask the clinical expert to ratify your preferred model? In addition, did you elicit information from experts about the nature of the hazard over time for each endpoint?

The question relates to the validation of extrapolations for ibrutinib TD, PFS and OS. Extrapolations have been validated by four clinicians, all national experts with experience in treating patients with WM in England. The clinicians' insights were gathered through a series of face-to-face 30-45 minute individual video calls, each involving one clinician and two Janssen employees, one from the Medical affairs and one from the Health economics and market access teams.

For TD, Janssen shared the graph presented as Figure 5 (p28) in the CS, which displayed the TD model projections for all the distributions. To assist with the interpretation of the projected curves, information was also provided about the percentage of patients who were still on treatment at different timepoints. Clinicians were then asked to select the curve which, based on their experience, seemed clinically most plausible.

Based on the most clinically plausible TD curve chosen, modelled PFS for ibrutinib was derived using the methods explained in Section A.8.2 of CS. Clinicians were shown a graph presenting the model projected PFS curves for ibrutinib and Physician's Choice (PC). Context was provided to explain the data sources and methods used to derive each curve for clarity. Janssen explained that PC PFS was derived based on an indirect treatment comparison (a ratio) using data from Study 1118E and the European Chart Review. To assist with the interpretation of the curves, information was also provided about the percentage of patients who

remained progression-free for each curve at different timepoints. Each clinician was subsequently asked to validate the plausibility of the modelled PFS curves and respective relative ibrutinib PFS benefit based on the difference between the ibrutinib PFS and the PC PFS curves (area between the two curves). The question was framed in a way that the clinicians could express their potential disagreement with the relative benefit as depicted by the modelled curves.

The same approach was followed to assess the clinical plausibility of the modelled ibrutinib relative OS benefit.

B5. PRIORITY. CS Appendices, Section B.5.2, page 48. The text states *"Visual inspection revealed that long-term extrapolations using Gompertz, generalised gamma, log-logistic and lognormal were unrealistic".* Please clarify who made these judgements – the clinicians or the company?

This question relates specifically to the ibrutinib PFS curves that were fitted to the RMR KM plot presented in Appendices Figure 9 (p48). The curves generated using different distributions were not shared with the clinicians. The curves fitted using the Gompertz, generalised gamma, log-logistic and lognormal were deemed "unrealistic" by Janssen as they suggested that ≥10% patients would still be progression-free and therefore alive 20 years after entering the model, despite patient age at model entry being 75 years of age. The patient age at model entry is in line with the SACT cohort median age when receiving ibrutinib. Furthermore, this is a fair exclusion of curves since it is clinically implausible for the model to predict patients with WM would still be progression-free after 20 years when median PFS from the RMR analysis is only xxxx months.

B6. PRIORITY: CS Appendices, Section B.5.3, page 50. The text states *"At 30 years, the survival projections of the generalized gamma, Gompertz, log-logistic and log-normal were judged unrealistic."* Please clarify who made these judgements - clinicians or the company?

This question relates specifically to the ibrutinib OS curves that were fitted to the SACT KM plot presented in Appendices Figure 11 (p50). The curves generated using different distributions were not shared with the clinicians. The rationale for deeming the generalized gamma, Gompertz, log-logistic and log-normal survival projections "unrealistic" is in line with that explained above for question B5. All these curves showed that over 10% of patients would still be alive 20 years after entering

the model. This is a fair exclusion of curves since it is clinically implausible for the model to predict patients with WM would survive longer than the general population.

B7. CS Appendices, Section B.5.1. With respect to the models fitted to data on time to TD, the exponential model was the worst-fitting model in terms of AIC and BIC, but it is selected for inclusion in the base case *"as the long-term projections were deemed to be closest to expected TD in clinical practice".* Please provide further detail on how this expectation of long-term TD was obtained.

As explained above in response to question B4, the curves fitted to the SACT TD KM plot were shared with the clinicians; the physicians were asked to choose the most clinically plausible curve based on their experience. The curve derived using the exponential distribution was overall retained as the most plausible curve for TD in English clinical practice.

B8. CS, Sections A.6.1 and A.6.2, page 18. The text states *"cross-source comparison of results for each outcome should be interpreted with caution."* The derivation of the HR for TD shown in Table 9 of the CDF-CS uses a cross-study comparison from SACT and RMR. Please comment on the reliability of this analysis. In addition, please clarify why PFS was not instead modelled by estimating the relationship between TD and PFS in RMR and then applying this to the TD function from SACT as a baseline.

The comment about cross-source comparison was made in Section A.6 where new and updated data gathered during the CDF data collection process was presented. By this, Janssen means that making naïve comparisons of results for the same outcome and across different data sources e.g. when looking at the graph overlays (for PPM: CS Figure 2 p21) or central values presented side by side in tables in this section (for PPM: Table 6 on p20), is likely to lead to misleading conclusions given differences in underlying patient baseline characteristics, study design etc.

Table 9 is presented in Section A.8 (p29) where Janssen explains how the subset of new evidence described in Section A.6 was used to model the new company BC. This table summarises the data and estimates derived from the SACT and the RMR datasets to model SACT PFS in the absence of PFS data in SACT. Table 9 specifically presents the breakdown of TD calculations used to estimate a hazard ratio (HR) for SACT TD "vs" RMR TD i.e. the ratio between SACT TD and RMR TD

that is applied to RMR PFS to derive SACT PFS. This is not a formal comparison of TD across the SACT and the RMR datasets.

In summary, Janssen does not consider highlighting the limitation of making cross-source comparisons in Section A.6 and leveraging data from different sources in Section A.8 a contradiction, provided the caveats of combining data from different sources has both been previously acknowledged and contextualised. As explained in the CS, it was necessary to combine data from different sources for this CDF Review given the scarcity of the new data collected, reflecting the rare nature of WM. Furthermore, the RMR population represents a subset of the SACT population. The approach used to derive the HR for TD leveraged the reported TD between two similar datasets which included a common population cohort. On this basis, the analysis is considered reliable.

The approach to modelling SACT PFS was anchored to RMR PFS and not SACT TD. RMR is the only data source for which robust data for both PFS and TD was available for the WM patients treated with ibrutinib described in the license (Study 1118E later data-cut only included a point estimate for TD). The intention of the modelling approach was to preserve the shape of the PFS curve reported for the RMR dataset, given the RMR population is a subset of the SACT cohort, by assuming that the difference between TD SACT and RMR TD would be similar for PFS.

B9. CS Appendices, Section B.5.2, page 47. The text states that *"Parametric curves were fitted using the method described by Guyot et al".* Is this referring to the generation of pseudo-IPD, rather than model-fitting?

This is correct. Parametric curves were fitted to RMR PFS, with the Guyot algorithm used to generate pseudo-IPD prior to curve fitting.

B10. PRIORITY: CS, Section A.6.3, page 23 Table 7. Given that on-treatment mortality data in SACT are available, which must be lower than PPM, please justify retaining the PPM value from the original data-cut of Study 1118E in the base case.

Following clarification with NICE and the ERG on 26 July 2021, Janssen agrees that should both on-treatment mortality (OTM) and PPM have been available from SACT, OTM would have been lower than PPM given the evidence suggests that the

relationship between TD and PFS is not equal, and that treatment discontinuation would occur ahead of progression. OTM is therefore deemed a proxy for PPM. Janssen considered using PPM data from the trial, in line with the FAD base-case, to be the most robust approach in the absence of SACT PPM data. Of note, two scenario analyses were conducted using SACT OTM (scenario #4) and RMR PPM (scenario #5) to assess the impact of using different data from the real-world setting. Whilst PPM was stated as a key area of uncertainty in the FAD, it is no longer a key driver of the ICER in this CDF review and the ICERs presented in the CS show the impact on the new company BC ICER is minimal (+£396/QALY and £1,398/QALY respective for scenario #4 and #5).

Adverse Events

B11. Appendices, Section B.1.2, Table 3. Several of the updated adverse event unit costs are considerably higher than those used in the FAD model. Please justify.

For adverse events (AEs), the FAD model applied a cost of £563.03 for management of pneumonia infection based on NHS Reference Costs 2014/15 (infections or other complications of procedures, without interventions, with CC Score 0-4 [WH07F – WH07G, costed as a weighted average of elective inpatient, non-elective inpatient (long and short stay) and day case attendances]). A cost of £162.02 was applied to all other AEs, based on NHS Reference Costs 2014/15 (estimated as a weighted average of non-admitted clinical haematology visit codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D).

For the CDF model, these costs were updated to more accurately reflect the actual AE costs incurred by the NHS, using Reference Costs for 2018/2019, for regular day or night admissions. Applying the updated AE costs (see CDF Submission Appendices, Table 3 p7) had a minimum impact on the results and reduced the new company BC ICER by £16/QALY.

Utility values

B12. CS Appendices, Section B.1.5, Table 8, page 22: A parameter is mentioned there 'Utility treatment increment' with value of [redacted] and SE of [redacted]. The ERG could not find any other mention of the parameter anywhere else in the submission, appendices, Excel model.

Please clarify whether you intended to use the parameter for deriving the cost-effectiveness evidence.

This parameter is not being used in the new company BC or in any scenario analysis for the CDF Review. Therefore, it is worth noting that the new company BC is conservative because a potential benefit associated with treatment with ibrutinib, an oral therapy, has not been accounted for.

Section C: Textual clarification and additional points

C1. CS, Section A.1, page 7. The text states *"SACT does not collect data on PFS" and later states "SACT data shows that 67% of patients had stopped treatment but had not progressed or died."* Given that SACT does not collect data on PFS, how can this latter statement be known?

The SACT database does not include a data collection field for progression as a time to event endpoint. However, based on information provided in Table 10, p23 of the SACT 3-year report, it does collect data on reasons for treatment discontinuation based on clinical judgement. Table 10 suggests that only 19% of patients discontinued treatment due to progression and that 14% of patients died on treatment (which could be accounted for as progression), equalling 33% in total. These data therefore indicate that 67% of patients have stopped treatment but have not progressed or died.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ibrutinib for treating Waldenström's macroglobulinaemia ID3778 rev [TA491]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Joint submission on behalf of Lymphoma Action and WMUK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Lymphoma Action** is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma. **WMUK**, a registered Charity in England and Wales, is a patient orientated organisation focused solely on those impacted by Waldenström's macroglobulinaemia. The goals of the charity are optimising access to accurate diagnosis & high-quality care, access to personalised information & support, access to new treatment, and research that matters to patients. WMUK directly interact with their members via support groups, webinars, individualised support and an annual summit.

	WMUK is primarily funded by charitable fundraising events and donations from patients, carers, family and friends, and other members of the general public. Some donations are received from pharmaceutical companies primarily to support events such as the charity's annual Patient / Doctor Summit.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Lymphoma Action: **Janssen**: £8,000 in 2021 and £20,000 in 2020 for sponsorship of education and training/survivorship events; publications; core services and covid19 **Roche**: £20,000 in 2021 for digital patient services; £20,000 in 2020 for sponsorship of education and training/survivorship events; publications; core services and covid19 WMUK: None
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	WMUK run a support group solely for Ibrutinib patients and their families and we have spoken to these patients at length to understand their experiences of being on this treatment versus other treatment regimens they may have had previously, including effectiveness, quality of life and side effects. We have also used information from UK-respondents to the Lymphoma Coalition's 2020 Global Patient Survey, which seeks to understand patient experience in lymphomas as well as the impact of treatment and care. A total of 679 people from the UK responded to the patient survey, 24% of whom had WM. An additional 64 people responded to the caregiver survey, 19% of whom cared for a person with WM. We also sent a survey to our network of patients and carers asking specifically, about their experience of current treatment for WM, with particular emphasis on quality of life. We received responses from three patients who had experience of ibrutinib treatment, which we have used in this submission. We have also included information based on our prior experience with patients with WM.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	WM is a rare and debilitating disease: with no established standard of care and the constant threat of relapse, a huge burden is placed on patients and their families. It is associated with a high unmet clinical need for new effective therapies. For many patients WM sadly forces them to stop working. A patient who had spent many years working as a Stage Manager had to give up his job as he lost track halfway through a performance due to poor concentration, something he had never previously done. He had always prided himself on having a sharp and analytical mind but found ~~on~~ during the three years he lived on 'active monitoring' he lived in a 'haze' often unable to complete simple tasks such as remembering meetings and appointments. WM develops over many months or years. It is associated with major disease-related symptoms that have a significant impact on the day-to-day lives of people with it. These include recurrent infections, weakness, extreme fatigue, breathlessness, and severe bone and joint pain. People with WM also report fevers, night sweats, weight loss, and significant reduction in their mobility. About 1 in 4 people with WM develop

peripheral neuropathy. This can cause tingling or numbness, usually in the fingers or toes, which, in turn, can affect fine motor skills and balance.

Complications arising in WM patients include:

- Cryoglobulinaemia (abnormal immunoglobulin proteins in the blood that can precipitate out into tissues at low temperatures): this can lead to kidney problems, joint pain, cold feet or hands, skin ulceration, and nerve damage.
- Cold agglutinin disease (a rare type of autoimmune hemolytic anemia in which the body's immune system mistakenly attacks and destroys its own red blood cells): this can cause fatigue, weakness, dizziness and headaches, back, leg, or joint pain, irritability or changes in behaviour, jaundice, vomiting or diarrhoea, cold feet or hands, chest pains or an irregular heartbeat. It can lead to anaemia. Recurrent transfusions and the iron overload that ensues, as well as an increased rate of venous thromboembolism, can all be acutely life-threatening.

In the Lymphoma Coalition's 2020 Global Patient Survey, just over half of patients (56%) reported that their lymphoma symptoms negatively impact on everyday activities that people their age can usually do.

Daily symptoms such as fatigue, which can be intense and disabling, have a negative impact on quality of life. Fatigue is consistently rated as the most common and the most disabling symptom of many types of lymphoma, including WM. Patients report that it has a negative impact on all aspects of life, including work, relationships, social activities, mood, sleep quality and overall enjoyment of life. 43% report stopping work or changing their working pattern because of their symptoms. This can also have a financial impact.

A patient who has had WM since 2008 told us, "When the lymphoma is more present and uncontrolled, it has a number of symptoms. Pains in the long bones of my body, extreme night sweats, breathlessness, lack of energy. It limits my ability to walk a distance or to walk up a hill or stairs. Heart flutters. Random skin rashes which have an intense itch which is continuous and drives me to distraction."

WM has a long disease trajectory, placing a significant burden on both the patient and family members/carers who must manage the consequence of side effects and the anxiety of anticipated relapses. Many WM patients and their families find themselves unable to go on holidays or make concrete

	plans for their future, they often have to reassess their plans for retirement and carers worry about how much 'caring' they will need to provide, if they themselves will be physically able to do so and the financial implications of having to pay for care. In addition, 'watch and wait' is described as particularly stressful by patients and their carers who must live with a high level of uncertainty, not knowing if or when they will need treatment. Having a diagnosis of cancer is life-changing and emotionally challenging. This burden is made heavier when patients are watching and waiting for symptoms to get worse and for treatment to start. Once patients do start treatment, they live with the constant threat of relapse and short or partial duration of response, as well as a high level of worry about what treatments will be available beyond first-line therapies. Carers play an important role in providing both emotional and practical support for people with WM. Most carers accompany their loved one to appointments, and almost half report having to take time off work. The psychological burden on carers is huge, with most reporting experiencing stress and anxiety, and in particular worrying about relapse. Three-quarters of carers report feeling tired or worn out and almost half feel their own health has suffered due to their caring responsibilities. A patient with WM who had to travel for treatment as part of a clinical trial, said, "I was lucky to have the support of family and friends with some logistics which helped and work were very flexible and supportive." Another patient with WM although living in Dorset, was treated at UCLH due to the rarity of the disease. For her husband it meant staying in hotels in London throughout her cycles of chemotherapy, so he could be there to support her. However, this was at considerable financial and emotional expense, and as he was away from the rest of the family he had no one on hand to support him when 'it all got too much' in the loneliness of a hotel room. For those who live alone without support they suffer both emotional and financial implications. A patient who was recently diagnosed told 'for a year prior to diagnosis I was in bed feeling exhausted. My employer sick pay ran out during treatment (~~9~~chemo) so I lost my job as I didn't feel well enough to return to work, I don't qualify for state pension for another two years, I don't qualify for any government support and live alone so WM has had a major financial impact on my life'.

	There is a significant psychological burden associated with WM, and patients frequently report emotional distress and poor mental health. Around 1 in 3 people with lymphoma report anxiety, particularly around relapse. One patient with WM said, “Living with lymphoma is a worry. Currently, it is incurable, I have it for life.” Another said, “In respect of emotional impact – just feel a bit ‘done in’ and don’t think I’ll ever be back to my ‘high energy previous self’.” One patient with WM told us, “I think I underestimate the effect on my husband… I don’t really think about him too much but I think he gets upset when he thinks back to what I once was.”
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is no established standard of care for WM and no previously licensed treatments *specifically* for treating WM. Prior to the introduction of BTK inhibitors such as ibrutinib, the most common options currently in use are a range of single and combination therapies that were developed for other lymphoproliferative diseases. The mainstay of therapies at front line and relapse are chemo-immunotherapy or to combine rituximab with a range of chemotherapy options. Whilst these therapies are effective at the outset, most patients relapse and need further lines of treatment. A patient who underwent several cycles of chemotherapy with Rituximab achieved only a ‘minor response’ in managing the disease ‘to say that the outcome of chemotherapy was disappointing is a gross understatement’. More recently many patients have been keen to avoid chemotherapy due to Covid risks, risks of visiting hospital to receive treatment and catch Covid and the risks of getting Covid with a compromised immune system. One patient stated ‘without Ibrutinib my prospects are pretty bleak with second line chemo or a stem cell transplant (with all the inherent complications) as my only alternatives, both of which I would struggle to cope with. Other patients talk of spending three weeks as a hospital inpatient for each of their cycles of chemotherapy (often 4-6 cycles) only for the treatment to be ineffective ‘I felt very poorly and my organs

	were beginning to be affected'. 'I relapsed in 2017 and received further chemotherapy but was intolerant to the Rituximab and lost consciousness during treatment'. Patients are restricted in the number of cycles of chemotherapy they can receive due to cumulative toxicity and for those presenting with WM at an earlier age, treatment options can rapidly become exhausted, leaving no effective therapies available. Patients stress how important and reassuring it is to have a number of lines of therapy available to postpone the point at which all treatments options have been exhausted, at which point the outcome is likely to be death from the disease. It should be noted that chemotherapy is often unsuitable for older people, amongst whom the disease is most prevalent, because of potential co-morbidities and the high toxicity of current treatments which leaves this group of patients particularly disadvantaged. In the Lymphoma Coalition's 2020 Global Patient Survey, 74% (n=120) of patients with WM had received chemo-immunotherapy. Half (51%) of them also received steroids. Just over half of patients reported that side effects of their lymphoma treatment negatively impacts on everyday activities and social activities that people their age can usually do. Fatigue, nausea and vomiting and recurrent infections are the side effects that patients report having the most impact on their lives. They are also concerned about a lack of long-term response to treatment, with over 4 in 10 worrying about relapse or disease progression. Chemotherapy options also have a risk of late effects such as second cancers, which are obviously a concern. One patient, who had had previous treatment with both chlorambucil and FCR, said, "The chemotherapy caused fatigue and nausea and was hard to cope with. The fatigue was hard to get through. I am also acutely aware that my immunity has been damaged by the chemotherapy and I am at extreme risk of opportune infections (Covid being the main one at the moment). This limits my lifestyle. I avoid crowded places as much as possible. It may stop me from going to cinemas, concert halls, theatres, etc. This is a constant worry for both myself and my wife."

	Treatment can also have practical and logistical impact on patients. One said, “I sorted out a schedule of getting to London, staying with a friend, organising work and attending the treatments. It was tiring but manageable.”
8. Is there an unmet need for patients with this condition?	Yes. The availability of a targeted, effective and well tolerated oral therapy is highly valued by patients and meets a significant unmet need amongst people with WM. With current covid circumstances and the uncertainty around protection with vaccines, the convenience of a treatment at home with no need for hospital visits or infusions should not be under estimated. Patients for who chemo immunotherapy is unsuitable have a particularly high unmet need. There is a limited range of therapies for WM, particularly for first-line treatment. Currently available options tend to lead to diminishing disease control after sequential use. There is a clear unmet need for an effective, well tolerated treatment that provides long-term disease control. Patients rated improved survival, ability to induce a remission, and quality of life as the top three criteria for any new treatment.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients consider ibrutinib a step change in managing WM. ‘Ibrutinib has proved to be a new lease of life, I have only limited side effects and my anaemia is being reversed’. Another patient states ‘after five years with initial chronic illness it is a great relief to be living a normal life now I’m on Ibrutinib, apart from remembering to take pills I can almost forget I have the disease. I’m very grateful to be on it and whilst the ongoing side effects can be a bit annoying they seem a very small price to pay for such an improved quality of life’. Patients feel the main advantage of ibrutinib is the potential for effective, durable disease control with minimal side effects. They also appreciate the convenience of an oral treatment that can be taken at home. A patient who was put on ibrutinib after previous treatments with chlorambucil and FCR said, “It is the best treatment I have had so far. Most of my blood counts have returned to be within the normal ranges for the first time in over 10 years. I am now able to go hill-walking without pains in my muscles, climb a hill, and

	generally enjoy life far more than when I had a high level of lymphoma." Another patient said, "Prior to taking ibrutinib as part of the Rainbow Trial cancer was present in about 80%-85% of my bone marrow and post [treatment cancer was present in] 10%-15% of my bone marrow... ~~o~~ obviously the impact on my life has been incredibly positive!" Many patients talk of a haze or 'brain fog' lifting after starting Ibrutinib and of improved energy levels and a general better sense of wellbeing. 'Overall it has been an amazing result in such a short period of time and my Consultant was amazed when after only two months the paraprotein dropped from 21 to 10'. Another patient on his seventh month of Ibrutinib states 'most of the symptoms I experienced before treatment have lessened to almost negligible levels. Night sweats and fiery skin sensation are now uncommon, itchy skin has reduced significantly and I have gone from using a skin cream daily to not using one in months'.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Like all treatments, patients are concerned about side effects, but patients who have had ibrutinib report these as easier to cope with than side effects of chemotherapy. Some worry about the ongoing nature of treatment, but generally feel that the advantages far outweigh the disadvantages. 'I was very fatigued when I started taking the drug and it was initially quite unpleasant, I had constant queasiness plus more severe nausea. I also suffered with chronic heartburn and indigestion whenever I ate. I also had some bruising on legs and feet and occasional burst blood vessels in my eyes. Ongoing I still get heartburn and have some digestive issues, mainly loose bowels, I have a lot of pills to remember but overall I'm very grateful to be on it'. Other consistent side effects reported via the group seem to be increased blood pressure, weight gain and mouth ulcers. A diagnosis of WM often means the end of 'normal' life as the patient knew it. Simple day to day tasks such as reading a newspaper or page of a book become impossible due to severe fatigue and an inability

	to concentrate. Weak and brittle nails, on first glance a minor side effect, cause such pain that it is impossible to pick up everyday items, resulting in a loss of independence and frustration. One patient reported being unable to pick up the pieces of jigsaw puzzles, a hobby that had helped her cope on the 'bad days' of her disease. One patient who has been on ibrutinib for WM since October 2020 said, "Side effects are minimal. There is no effect on the healthy tissues of my body, unlike chemo. The only side effect which was problematic was the irregular heart rhythms. They have now settled down to a less frequent occurrence and I have got used to them." Another, who described side effects of hair loss, spots, bruising and swollen ankles, said, "It's a pain to have to take some many drugs every day and the side effects can be a bit draining / debilitating – but a small price for enjoying a pretty full life."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Ibrutinib is particularly valuable for patients with disease that was resistant to first line immunotherapy or who relapsed following a successful first line therapy. WM is a condition also with a greater prevalence in older people and Ibrutinib is particularly beneficial for this group~~,~~ as existing treatments have high toxicity levels and often adverse reactions that are less likely to be tolerated by older people. Ibrutinib is also a realistic alternative to stem cell transplant for some patients. This is clearly a huge advantage as it is an easy to take oral tablet rather than several months of treatment with unpleasant and sometimes life threatening side effects and hospital admissions.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Again existing treatments are less likely to be tolerated by older people and as WM is a condition with a greater prevalence amongst older people Ibrutinib would be particularly beneficial for this patient population.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Given the ongoing COVID-19 pandemic, it is more important than ever to consider the potential benefits of well tolerated treatments that can be administered orally at home. There is also no established standard of care for WM and no previously licensed treatments specifically for treating this disease.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Patient's regard Ibrutinib as a step change in treatment and life transforming drug that has dramatically improved their quality of life, allowing them to participate in general day to day activities and very quickly return to a 'normal' life, including work and socialising and returning to favourite hobbies and activities. The effect on their WM symptoms was almost immediate and symptoms quickly came back if treatment had to be paused.	

- A targeted therapy is highly valued by patients and addresses a significant unmet need. Ibrutinib is a novel treatment with a completely different mechanism of action to existing treatments, it is highly effective compared with existing treatments and very well tolerated with a much lower toxicity profile. Ibrutinib is the first technology with specific licence to treat this rare condition.
- Current treatment options generally provide short-term remissions and cause significant side effects and options for those patients who relapsed are limited. Chemo-immunotherapy needs to be delivered in a hospital setting. The fact that ibrutinib is administered orally means it can be taken at home, saving outpatient appointments. This is particularly important during the ongoing COVID-19 pandemic, when vulnerable patients are reluctant to attend healthcare settings.
- The side effects of Ibrutinib are much less severe and can be much better tolerated in an older population, where the disease is most prevalent. It provides another treatment option for WM patients who have a high unmet clinical need for new effective therapies.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Ibrutinib for treating Waldenström's macroglobulinaemia ID3778 rev [TA491]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Representing Royal College Pathologists and British Society Haematology**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): trustee of national charity for patients with WM
5a. Brief description of the organisation (including who funds it).	
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**no**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim of treatment is to control the disease, to prolong life and to lead to better quality of life by reducing some of the symptoms of the disease and its complications. Any treatment choice should take into consideration that a lot of morbidity and mortality associated with WM is not due to the WM itself but other causes which may be indirectly related, e.g. infection risk, complications of treatment. (Castillo et al BJHaem 2015 169: 81-89)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Response in clinical trials is based on international working group guidelines on response assessment (Owen 2013 160:171-176) primarily based on reduction in paraprotein level. However on a clinical day-to-day perspective I would say there are two aspects to this question that are clinically significant and equally important. Firstly, the indication for which the treatment was being given in the first place and its resolution- e.g. if treatment was commenced for hyperviscosity symptoms related to a high paraprotein, then reduction in paraprotein is very important, however, if it was for symptomatic anaemia, then the more clinically relevant factor is the improvement in haemoglobin rather than level of paraprotein reduction. Given the clinical symptoms and indications for treatment can be very varied, this makes this aspect quite difficult to

	summarise for all patients due to the number of rare complications that can occur all of which can be an indication for treatment. The second aspect of clinically significant treatment response is length of time to next treatment. There is some evidence that depth of response with chemoimmunotherapy is predictive of progression-free survival and time to next treatment, however this may not be the case with all therapies, for example, whilst those who achieve a PR with ibrutinib have been reported to have a better PFS than those who achieve less than a PR, achieving a better response (very good partial response) did not result in further improvement in PFS in one retrospective study (Castillo et al BJHaem 2021 Feb;192(3):542-550.)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is with current treatments available to patients on the NHS. The only option available is chemoimmunotherapy which can be effective for some patients, but may of our patients are older and frailer and thus may not be suitable for chemoimmunotherapy. Toxicity can be a concern with chemoimmunotherapy including risk of infection and secondary malignancies. We know that giving multiple lines of different chemotherapeutic regimens can lead to shorter times to next line of therapy with increasing concern about toxicity. I reiterate that many of these patients will die due to other causes rather than WM directly and so it is important to be able to give a treatment that could provide may patients a well tolerated oral option that can lead to meaningful and durable responses to their disease but minimise toxicity.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Waldenstrom Macroglobulinaemia (WM) is a rare B cell lymphoproliferative disorder. Patients are typically elderly (median age approx. 70 years at diagnosis) and symptoms occur as a consequence of bone marrow failure due to lymphoma infiltration, due to nodal disease or due to specific complications related to the IgM monoclonal protein produced by the lymphoma cells. The most common symptoms requiring therapy are anaemia, peripheral neuropathy and hyperviscosity syndrome. WM typically follows a relapsing

	and remitting course over many years and as a consequence patients will receive many different forms of chemotherapy. There is no consensus on standard of care for initial therapy in WM. Internationally, and where available, choices of therapy include rituximab monotherapy, chemoimmunotherapy regimens, proteasome inhibitor containing regimens and BTK inhibitors. In the UK, frontline, the two most frequently used chemoimmunotherapy regimens used at present are R-bendamustine based on Rummel et al 2013 Lancet 1203-1210 and DRC (dexamethasone, rituximab and cyclophosphamide) based on a phase 2 study (JCO 2007 25(22):3344-9). There are no prospective trials comparing the two regimens, however clinical practice and retrospective evidence seem to suggest that R-bendamustine is associated with quicker, deeper and perhaps more prolonged responses but with added potential toxicity risks both short term (eg. Infections) and longer tem (e.g. secondary MDS). Treatment in the relapsed/ refractory setting is more varied and depends on again disease related factors, previous treatment, length of time of response to prior therapy, patient related factors. However, the majority of patients have been commenced on ibrutinib since its availability on the CDF. Prior to this, it would have been alternative chemoimmunotherapy regimens.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are national guidelines by BCSH- however the current guidelines (Owen 2014) predate the clinical licensing of ibrutinib for WM. Updated guidelines are currently in the final stages of peer review and will be published in the near future. There are also ESMO guidelines (Kastritis et al 2018 Annals of Oncology 29 (S4): iv41-iv50 and international consensus guidelines (Castillo et al Lancet Haematology 2020 e827-837) both of which include ibrutinib (with or without rituximab) as a treatment option for patients with symptomatic WM requiring therapy.
• Is the pathway of care well defined? Does it vary or are there	Given that there are no large trials in WM, there can be variability in how patients are treatment both nationally (in terms of chemoimmunotherapy choice) and then internationally where more treatment options may be available. There is no one standard well defined pathway of care. However, there is general consensus that at present chemoimmunotherapy choices in practice in the first line setting are most

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	commonly either rituximab-bendamustine or dexamethasone rituximab and cyclophosphamide. Second line therapy currently most often given is ibrutinib via CDF but prior to the availability of this, would be an alternative chemoimmunotherapy regimen or clinical trial. A small proportion of patients may be considered for autologous stem cell transplant in the relapsed setting but this is only an option for younger, fitter patients and its role now that there are other options such as BTK inhibitors becomes less clear even in this cohort.
• What impact would the technology have on the current pathway of care?	I believe this technology would have a massive impact for patients with WM, and it would be a big step backwards not to offer it as an option for patients requiring therapy. Many patients are older frailer and in the relapsed and refractory setting would not be suitable for second line chemoimmunotherapy options, whereas this would give them an option of a drug that could potentially lead to improvement in the quality and quantity of life expected. Even in those patients fit enough for further chemotherapy, the expected time to next treatment is shorter and associated with increased toxicity and so this would provide an alternative method of treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, we have vast experience in the use of this drug and I expect any hospital treatment patients with blood cancers will also be very used to giving it. It has been licensed and funded for another haematological malignancy (CLL) for many years and so there is a great deal of experience in monitoring patients who are taking it. It has also been given to a number of patients via the CDF to patients with WM in specific with no new toxicity signals in this disease in specific.
• How does healthcare resource use differ between the technology and current care?	I anticipate this technology would use less healthcare resource as it is an oral therapy as opposed to intravenous chemoimmunotherapy options which require daycare space and nursing time as well as intravenous access. This treatment lends itself also to virtual monitoring, and patients can be reviewed for some of their consultations virtually.
• In what clinical setting should the technology be used? (For example,	Secondary care clinics i.e. haematology clinics in hospital for prescribing, monitoring of efficacy and toxicity. However primary care should be alerted to potential toxicity concerns for support in monitoring and management of toxicities if and when they occur. E.g. hypertension, potential drug interactions

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil as it is used widely already
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes for the reasons stated above. Chemoimmunotherapy regimens in the relapsed and refractory setting are known to be associated with increased toxicity and shorted progression free survival times. This is a technology that we know is very active in WM, and would provide meaningful durable responses for patients based on clinical trial data.
• Do you expect the technology to increase length of life more than current care?	Yes for the reasons stated above.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes for the reasons stated above

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	N/A
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No. Prophylactic antibiotics/ antivirals can be given with ibrutinib to try and reduce risk of infection. Some new medication may need to be prescribed if any complications develop e.g. hypertension. There needs to be an awareness of the risk of bleeding/bruising due to platelet dysfunction and patient education regarding both this and to always review concomitant medication to ensure no interactions.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No. If there is a patient requiring therapy, and ibrutinib is deemed suitable and available and the treatment choice, then this would continue for as long as the patient is responding and until next line of therapy required or if there is toxicity from the drug.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As above, due to the indication for treatment being quite varied and the impact of these complications on cost per QALY being therefore varied, it is even more difficult to estimate. E.g. reduction in admissions for those with recurrent infections, reduction in transfusion requirements etc.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes. It is generally well tolerated drug that offers patients a more targeted approach of treatment of their WM. It has a relatively quick time to action and so can help relieve symptoms of patients very quickly. It also has in trials and real world evidence, prolonged PFS that can have a substantial impact for the patient. It avoids patients having to come into hospital so frequently for intravenous therapy.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, first in class and first targeted therapy licensed for use in WM
• Does the use of the technology address any particular unmet need of the patient population?	Tolerated by patients who are old and frail who may not be suitable for chemoimmunotherapy
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	A proportion of patients will discontinue the therapy for toxicity related reasons, and some patients will require further medication due to side effects of the therapy. Toxicity can include: Arthralgias, GI disturbance, risk of infection, cardiac risk including atrial fibrillation and hypertension, bleeding risk and risk of cytopenias. Overall, however the therapy is well tolerated by the majority of patients.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The two largest prospective trials examining the use of ibrutinib in WM in the relapsed/refractory setting are: Treon et al NEJM 2015 372:1430-1440 with long term follow up JCO 2000 39: 565-575. With 5 year follow up, the median PFS is not reached in this study in the 63 patients entered. They postulated that single agent ibrutinib is not as effective for those with MYD88 wild type disease, however this was based on only 4 patients. Toxicities were as seen in other trials using ibrutinib and as seen in everyday practice. The second study was the innovate trial which looked at the use of ibrutinib in combination with rituximab versus rituximab alone for previously treated patients with WM. Dimopoulos NEJM 2018; 378:2399-2410 Whilst this study was looking at the combination of rituximab with ibrutinib there was a substudy which looked at single agent ibrutinib in those who were refractory to rituximab. (Trotman et al CCR 2021 online ahead of print). This part of the study recruited 31 patients who had either been refractory to their last line of rituximab containing regimen or relapsed within 12 months, after median follow up of just under 5 years, median PFS is 39% with 5 year PFS of 40%.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	It should be noted that primary endpoint in these trials is PFS, but there will be further time until next line of therapy which is perhaps more clinically relevant. There is good data on improvement of both IgM levels and haemoglobin both of which are clinically relevant from a morbidity perspective. Overall survival is also important and reported in both trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Response rates are reported but as discussed may not adequately reflect PFS. PFS is also reported in these studies.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to the best of my knowledge.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	WM is a rare disease with very few clinical trials specifically in this disease and most of these are in the frontline setting. Given the median age of patients at diagnosis is over 70, trials that report on the use of chemoimmunotherapy in the relapsed/refractory setting are going to be skewed to the fitter patient population.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	My personal experience is that the real world echos what we have seen in trials. This has also been seen by other groups who have noted similar efficacy and toxicity signals as has been reported in trials (Castillo et al *HemaSphere*. 2020; 4: e363)
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	This is a disease primarily of the older age group, who are vulnerable to multiple complications, and so this oral therapy represents an important addition to treatment options.

22b. Consider whether these issues are different from issues with current care and why.	No.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Effective non chemoimmunotherapy option for patients with relapsed or refractory WM
- Leads to improved expected PFS compared to chemoimmunotherapy in second line setting
- Well tolerated for majority of patients
- May be an option for patients not suitable for further chemoimmunotherapy
- It is standard treatment internationally based on strong evidence (by WM standards) of its efficacy

Thank you for your time.

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Public Health England

Protecting and improving the nation's health

Ibrutinib for treating Waldenström's macroglobulinaemia – data review

Commissioned by NHS England and NHS Improvement

Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of ibrutinib for Waldenström's macroglobulinaemia. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended commissioning of ibrutinib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of ibrutinib in the CDF population, during the managed access period. This report presents the results of the use of ibrutinib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 70% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for ibrutinib for Waldenström's macroglobulinaemia in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 28 September 2017 and 27 September 2020, 909 applications for ibrutinib were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figure 1 and Figure 2), 823 unique patients, who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS) (1).

Results

823 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 24.9 months [95% CI: 21.8, 28.9] (757 days). 79% of patients were still receiving treatment at 6 months [95% CI: 76%,82%], 67% of patients were still receiving treatment at 12 months [95% CI: 64%, 71%], 58% of patients were still receiving treatment at 18 months [95% CI: 54%, 62%], 51% of patients were still receiving treatment at 24 months [95% CI: 47%, 55%] and 38% of patients were still receiving treatment at 36 months [95% CI: 32%, 43%].

At data cut off, 45% (N=368) of patients were identified as no longer being on treatment. Of these 368 patients, 19% (N=71) of patients stopped treatment due to progression, 13% (N=48) of patients stopped treatment due to acute toxicity, 7% (N=25) of patients chose to end their treatment, 27% (N=100) of patients died not on treatment, 14% (N=53) of patients died on treatment, 2% (N=8) of patients completed treatment as prescribed and 17% (N=63) of patients did not have a treatment record in SACT in at least 4 months and are assumed to have completed treatment.

The median OS was not reached. OS at 6 months was 91% [95% CI: 89%, 93%], OS at 12 months was 84% [95% CI: 81%, 87%], OS at 18 months was 77% [95% CI: 74%, 80%], OS at 24 months was 73% [95% CI: 69%, 76%] and OS at 36 months was 61% [95% CI: 56%, 65%].

A treatment duration sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

A secondary sensitivity analysis was conducted to show on treatment mortality. The median OS was not reached

A third sensitivity analysis was carried out on treatment duration and OS to evaluate outcomes by prior lines of therapy. Results for treatment duration showed a difference of 11.8 months between those who received 1 to 3 prior lines and those who received more than 3 prior lines (1 to 3 prior lines cohort = 26.5 months; more than 3 prior lines cohort = 14.7 months). The median OS was not reached amongst those who received 1 to 3 prior lines with the median OS being 28.5 months amongst those who received more than 3 prior lines.

Conclusion

This report analysed SACT real world data for patients treated with ibrutinib for Waldenström’s macroglobulinaemia in the CDF. It evaluates treatment duration, OS and treatment outcomes for all patients treated with ibrutinib for this indication.

Introduction

Waldenström's macroglobulinaemia (C88.0) accounts for <1% of all cancer diagnoses in England. In 2018, 397 patients were diagnosed with Waldenström's macroglobulinaemia (males 259, females 138) (2).

Ibrutinib is recommended for use in the Cancer Drugs Fund as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least one prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed (3).

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England (4). From 29 July 2016, NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period (5).

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of ibrutinib for treating Waldenström's macroglobulinaemia [TA491]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of ibrutinib (Janssen) in treating Waldenström's macroglobulinaemia [TA491] and published guidance for this indication in November 2017 (6).

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of ibrutinib through the CDF for a period of 36 months, from September 2017 to September 2020.

During the CDF funding period, results from SACT are likely to answer the main clinical uncertainties raised by the NICE committee.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for ibrutinib for Waldenström's macroglobulinaemia in England, during the CDF funding period.

As part of the guidance review, Janssen will provide supportive data from 2 clinical trials, the phase II registration study 1118E and the phase III study 1127 (iNNOVATE, arm C only) (7, 8). Additional supportive evidence from the Rory Morrison UK Clinical Registry may be considered as a valuable addition to the clinical evidence base and may resolve some of the clinical uncertainties (9).

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection:

1. **Treatment duration** for the use of ibrutinib
2. **Overall survival** from the start of a patient's first treatment with ibrutinib
3. **On treatment mortality** - the number of deaths that occur while on treatment with ibrutinib

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Janssen) formed a working group to agree the Data Collection Agreement (DCA) (6). The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of ibrutinib. It also detailed the eligibility criteria for patient access to ibrutinib through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for ibrutinib, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Ibrutinib clinical treatment criteria

- Application made by, and first cycle of systemic anti-cancer therapy to be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Confirmed clinicopathological diagnosis of Waldenström's macroglobulinaemia and meets criteria using consensus panel criteria from the Second International Workshop on Waldenström's macroglobulinaemia (7)
- Documented progression of disease or no response to previous line of systemic therapy

- Symptomatic disease and meets at least one of the recommendations for requiring active treatment as set out in the Second International Workshop on Waldenström's macroglobulinaemia (8)
- Patient has received at least 1 prior line of treatment
- Patient has never received any B cell receptor therapies (for example, ibrutinib, acalabrutinib)
- Ibrutinib is to be used as a single agent
- Ibrutinib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment
- Performance status of the patient is 0, 1 or 2
- Patient's neutrophil count is greater than or equal to 1 x 10^9/L
- Patient's platelet count is greater than or equal to 50 x 10^9/L
- Patient is not on concurrent therapy with warfarin or CYP3A4/5 inhibitors
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)
- Ibrutinib to be otherwise used as set out in its Summary of Product Characteristics

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If 2 trusts apply for ibrutinib for the treatment of Waldenström's macroglobulinaemia for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If 2 trusts apply for ibrutinib for the treatment of Waldenström's macroglobulinaemia for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If 2 applications are submitted for ibrutinib for the treatment of Waldenström's macroglobulinaemia and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

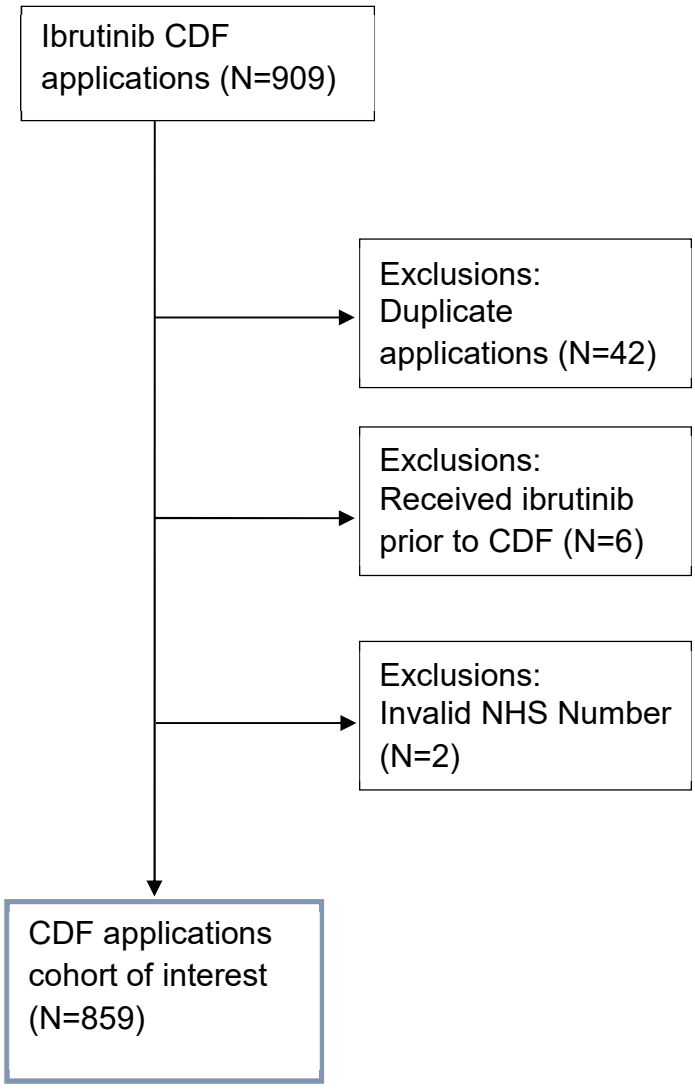
The analysis cohort is limited to the date ibrutinib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 28 September 2017 and 27 September 2020. A snapshot of SACT data was taken on 6 March 2021 and made available for analysis on 12 March 2021 and includes SACT activity up to the 30 November 2020. Tracing the patients' vital status was carried out on 29 March 2021 using the personal demographics service (PDS) (1).

There were 909 applications for CDF funding for ibrutinib for Waldenström's macroglobulinaemia between 28 September 2017 and 27 September 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 867 unique patients.

Six patients were excluded from these analyses as they appeared to have received ibrutinib prior to the drug being available through the CDF and 2 were excluded as they had an invalid NHS number.

Figure 1. Derivation of the cohort of interest from all CDF (Blueteq) applications made for ibrutinib for treating Waldenström's macroglobulinaemia between 28 September 2017 and 27 September 2020



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for ibrutinib in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items (10) used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34) (10) are used to identify a patient's final treatment date. The latest of these 3 dates is used as the patient's final treatment date. Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the first and eighth day, but nothing on days 2 to 7 and days 9 to 20. The first day would be recorded as the 'start day of cycle'. The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the first and eighth day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Ibrutinib is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 28 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next (11). Ibrutinib is a 28-day cycle consisting of one administration of 28 tablets.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the censor date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patient's date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61
- there is no further SACT records for the patient following a 4-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.
All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

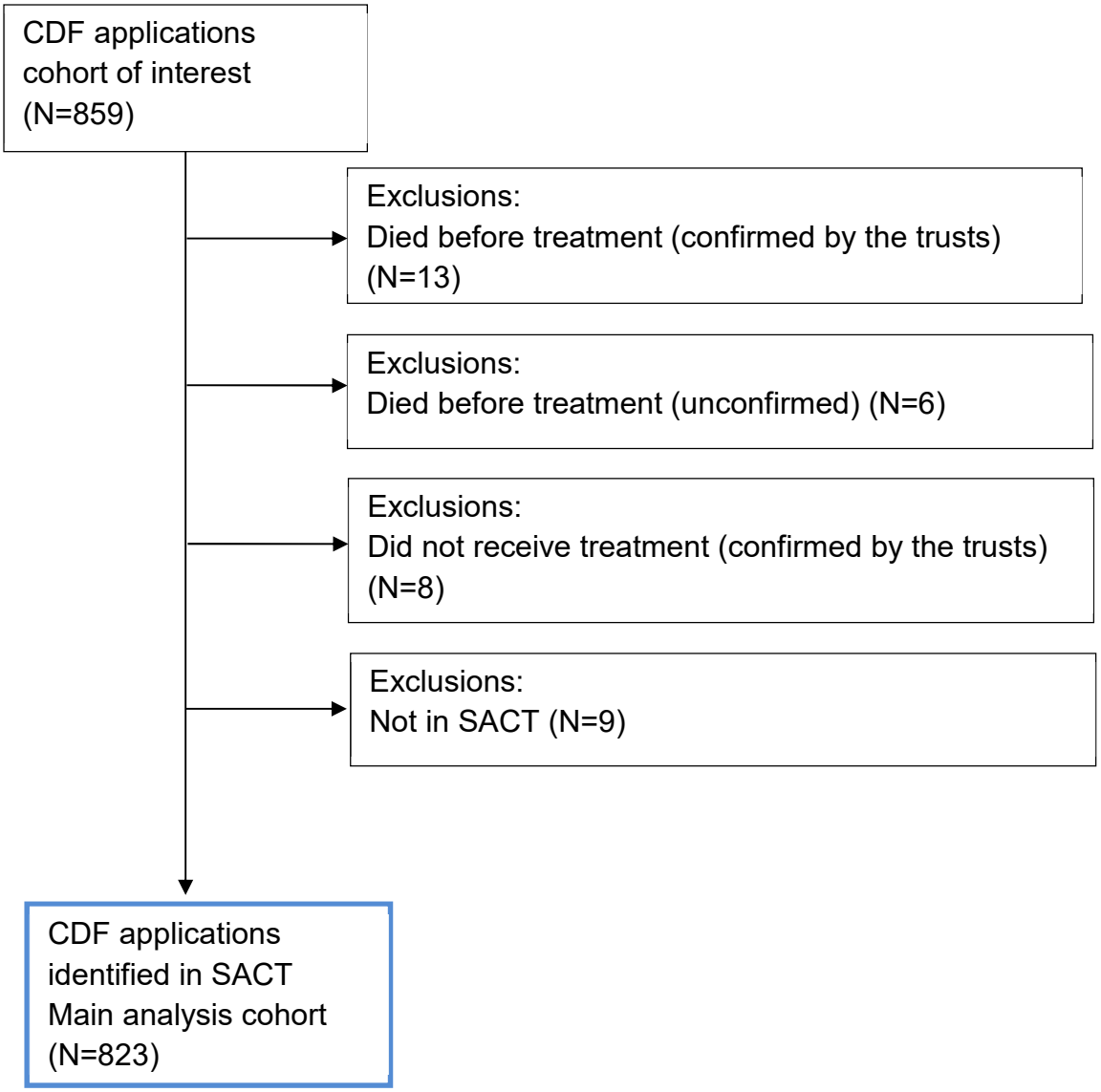
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 859 new applications for CDF funding for ibrutinib for Waldenström's macroglobulinaemia, 8 patients did not receive treatment, 19 patients died before treatment and 9 patients were missing from SACT[a] (see Figure 2).

Figure 2. Matched cohort - SACT data to CDF (Blueteq®) applications for ibrutinib for Waldenström's macroglobulinaemia between 28 September 2017 and 27 September 2020



[a] Of the 8 patients that did not receive treatment, all were confirmed by the relevant trust by the PHE data liaison team. Of the 19 that died before treatment, 13 have been confirmed by the relevant trusts by the PHE data liaison team, 6 patients were followed up by the data liaison team but the relevant trust did not confirm if the patient died before treatment.

A maximum of 832 ibrutinib records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 99% (823 out of 832) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 73% complete.

Table 1. Completeness of key SACT data items for the ibrutinib cohort (N=823)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	73%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for the outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with ibrutinib in at least 4 months (10). These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 368 patients. Of these, 257 (70%) have an outcome summary recorded in the SACT dataset.

Table 2. Completeness of outcome summary for patients that have ended treatment (N=368)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	70%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Each Blueteq data item was 100% complete.

Table 3. Completeness of key Blueteq data items for the ibrutinib cohort (N=823)

Variable	Completeness (%)
Prior lines of therapy	100%
Previous treatments	100%
Progression	100%

Patient characteristics

The median age of the 823 patients receiving ibrutinib for treating Waldenström's macroglobulinaemia was 75 years; and was consistent for both genders.

Table 4. Patient characteristics (N=823)

Patient characteristics[b]			
		N	%
Sex	Male	544	66%
	Female	279	34%
Age	Under 40	1	under 1%
	40 to 49	11	1%
	50 to 59	53	6%
	60 to 69	171	21%
	70 to 79	322	39%
	80+	265	32%
Performance status	0	186	23%
	1	283	34%
	2	117	14%
	3	14	2%
	4	1	under 1%
	Missing	222	27%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items: prior lines of therapy, progression and previous treatments. See Appendix A for previous treatment full form.

Table 5. Distribution of key Blueteq data items (N=823)

Blueteq data items[c]			
		N	**%**
Prior Lines of therapy	1	499	61%
	2	194	24%
	3	73	9%
	4	30	4%
	5	20	2%
	5+	7	1%
Progression	After response to previous line of therapy	645	78%
	No response to previous line of systemic therapy	178	22%
Previous treatment	BR	182	22%
	DCR	175	21%
	Other	144	17%
	Cb mono	114	14%
	R mono	80	10%
	CbR	48	6%
	FCR	38	5%
	B mono	24	3%
	Bort R	11	1%
	CladR	7	1%

[c] Figures may not add to 100% due to rounding.

Treatment duration

Of the 823 patients with CDF applications, 368 (45%) were identified as having completed treatment by 30 November 2020 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with ibrutinib in at least 4 months (see Table 10). The median follow-up time in SACT was 12.9 months (392 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal 2 months after the month's treatment activity has ended; this provides a maximum follow-up period of 38 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 39 months. SACT follow-up ends 30 November 2020.

Table 6. Breakdown by patients' treatment status[d,e,f]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	180	22%
Patient died – on treatment	53	6%
Treatment stopped	135	16%
Treatment ongoing	455	55%
Total	**823**	**100%**

Table 7. Treatment duration at 6, 12, 18, 24 and 36 month intervals

Time period	Treatment duration (%)
6 months	79% [95% CI: 76%, 82%]
12 months	67% [95% CI: 64%, 71%]
18 months	58% [95% CI: 54%, 62%]
24 months	51% [95% CI: 47%, 55%]
36 months	38% [95% CI: 32%, 43%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration for all patients was 24.9 months [95% CI: 21.8, 28.9] (757 days) (N=823).

[d] Figures may not sum to 100% due to rounding.
[e] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website.

Figure 3. Kaplan-Meier treatment duration (N=823)

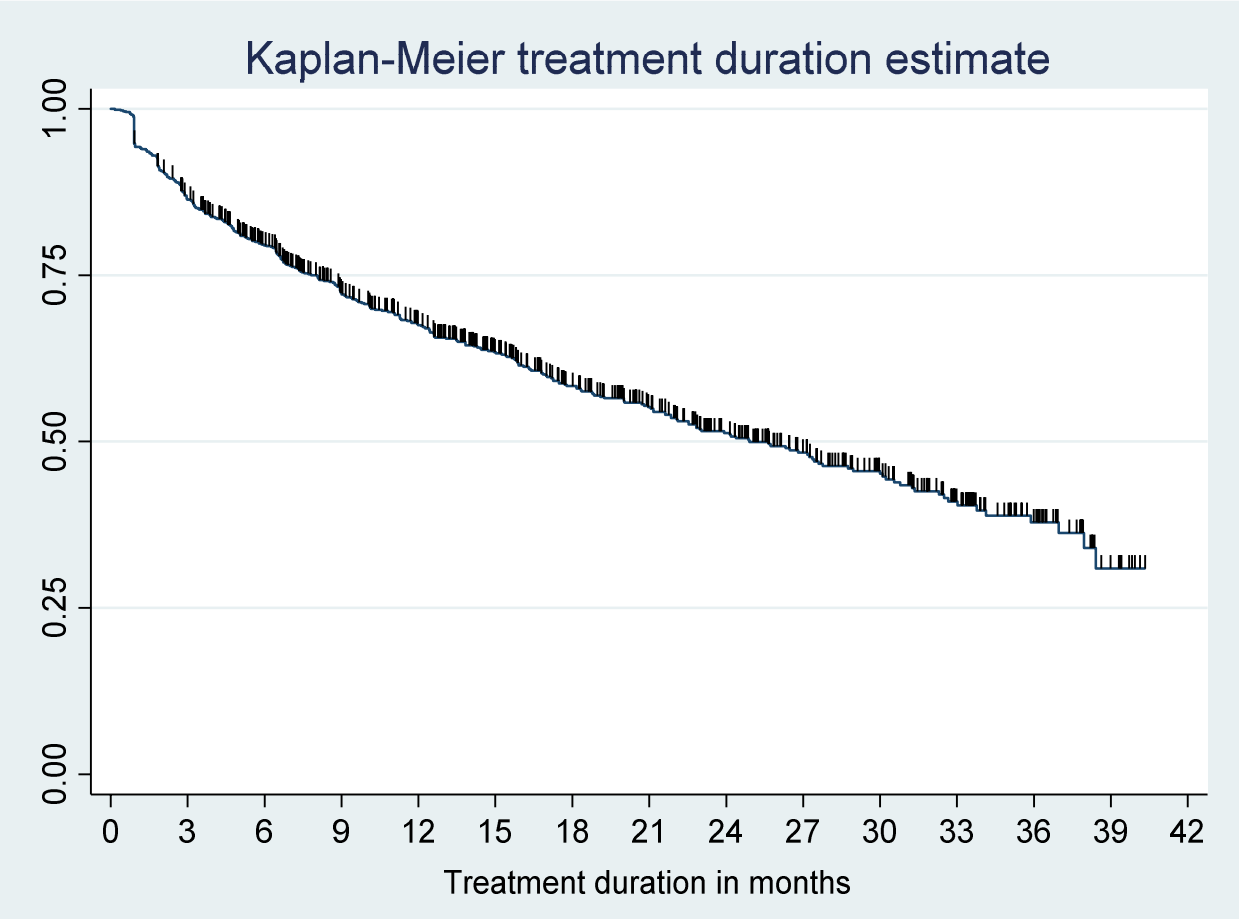


Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 38 months (1,156 days). SACT contains more follow-up for some patients.

Table 8. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Number at risk	823	698	597	500	434	356	291	241	194	146	110	71	36	8

Table 9 shows that for all patients who received treatment, 455 were still on treatment (censored) at the date of follow-up and 368 had ended treatment (events).

Table 9. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Censored	455	442	395	349	316	263	225	190	159	121	94	64	33	8
Events	368	256	202	151	118	93	66	51	35	25	16	7	3	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 45% (N=368) of patients had ended treatment at 30 November 2020.

Table 10. Treatment outcomes for patients that have ended treatment (N=368)[g],[h]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	71	19%
Stopped treatment – acute toxicity	48	13%
Stopped treatment – patient choice	25	7%
Stopped treatment – died not on treatment[i]	100	27%
Stopped treatment – died on treatment	53	14%
Stopped treatment – completed as prescribed[j]	8	2%
Stopped treatment – no treatment in at least 4 months	63	17%
Total	**368**	**100%**

Table 11. Treatment outcomes and treatment status for patients that have ended treatment (N=368)

Outcome[k]	Patient died [l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	44	27	
Stopped treatment – acute toxicity	21	27	
Stopped treatment – patient choice	11	14	
Stopped treatment – died not on treatment	100		
Stopped treatment – died on treatment			53

[g] Figures may not sum to 100% due to rounding.
[h] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[i] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.
[j] Of the 8 patients that completed treatment as prescribed, reasons ranged from patient proceeded to a stem cell transplant, changing regimen or treated for a second primary cancer.
[k] Relates to outcomes submitted by the trust in table 10.
[l] Relates to treatment status in table 6 for those that have ended treatment.

Outcome[k]	Patient died [l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – completed as prescribed	4	4	
Stopped treatment – no treatment in at least 4 months		63	
Total	**180**	**135**	**53**

Overall survival (OS)

Of the 823 patients with a treatment record in SACT, the minimum follow-up was 6 months (182 days) from the last CDF application. Patients were traced for their vital status on 29 March 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 19 months (578 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12. OS at 6, 12, 18, 24 and 36 month intervals

Time period	OS (%)
6 months	91% [95% CI: 89%, 93%]
12 months	84% [95% CI: 81%, 87%]
18 months	77% [95% CI: 74%, 80%]
24 months	73% [95% CI: 69%, 76%]
36 months	61% [95% CI: 56%, 65%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 29 March 2021. The median survival was not reached.

Figure 4. Kaplan-Meier survival plot (N=823)

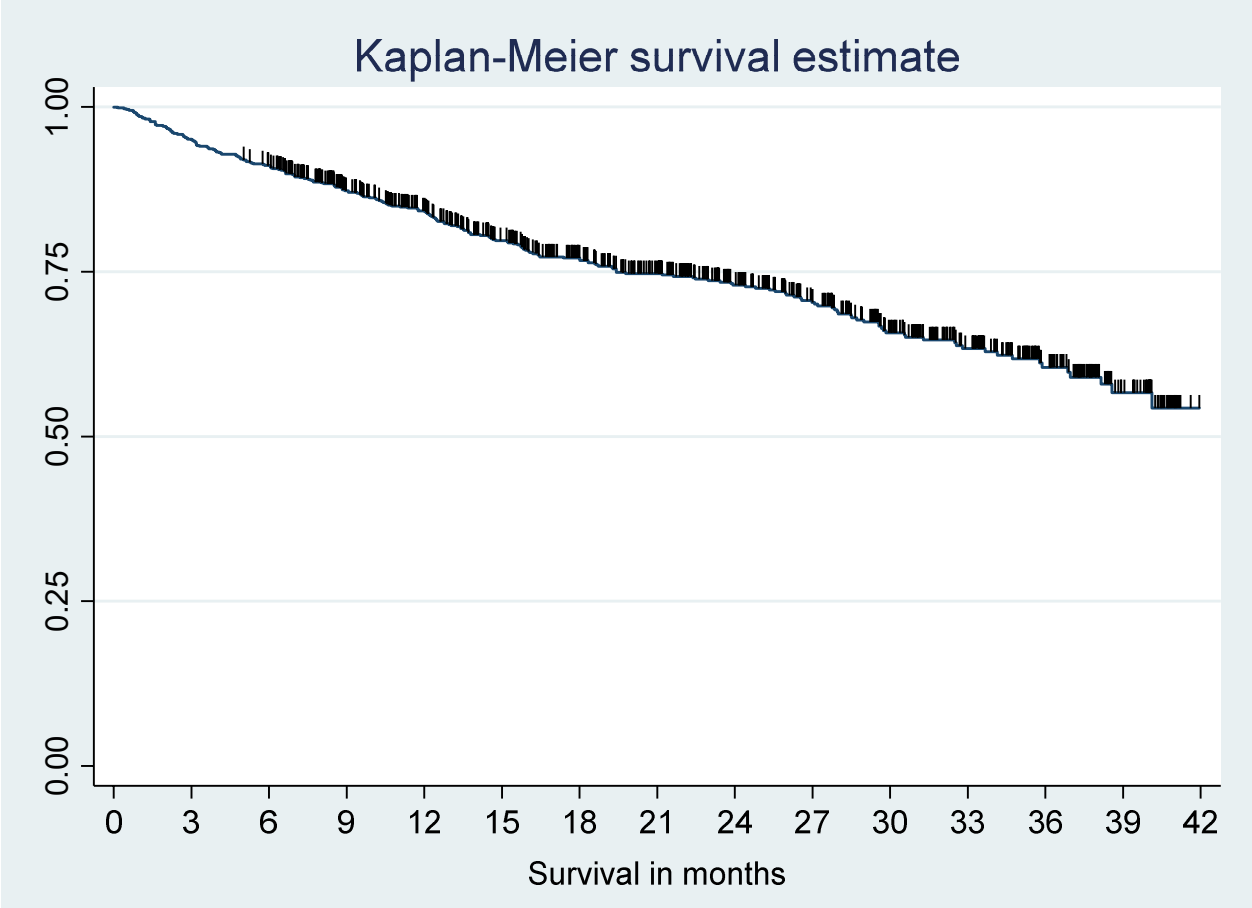


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 42 months (1,278 days), all patients were traced on 29 March 2021.

Table 13. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Number at risk	823	783	745	647	576	501	436	376	316	254	192	143	92	39

Table 14 shows that for all patients who received treatment, 590 were still alive (censored) at the date of follow-up and 233 had died (events).

Table 14. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Censored	590	590	585	517	468	423	374	327	275	223	176	133	87	38
Events	233	193	160	130	108	78	62	49	41	31	16	10	5	1

Sensitivity analysis

6-months SACT follow-up

Treatment duration

Sensitivity analysis was carried out on a cohort with at least 6 months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 28 September 2017 to 30 May 2020 and SACT activity was followed up to the 30 November 2020.

Following the exclusions above, 724 patients (88%) were included in these analyses. The median follow-up time in SACT was 14.7 months (447 days)

The Kaplan-Meier curve for ongoing treatment is shown in Figure 5. The median treatment duration for patients in this cohort was 24.9 months [95% CI: 21.6, 28.9] (757 days) (N=724).

Figure 5. Kaplan-Meier treatment duration plot (N=724)

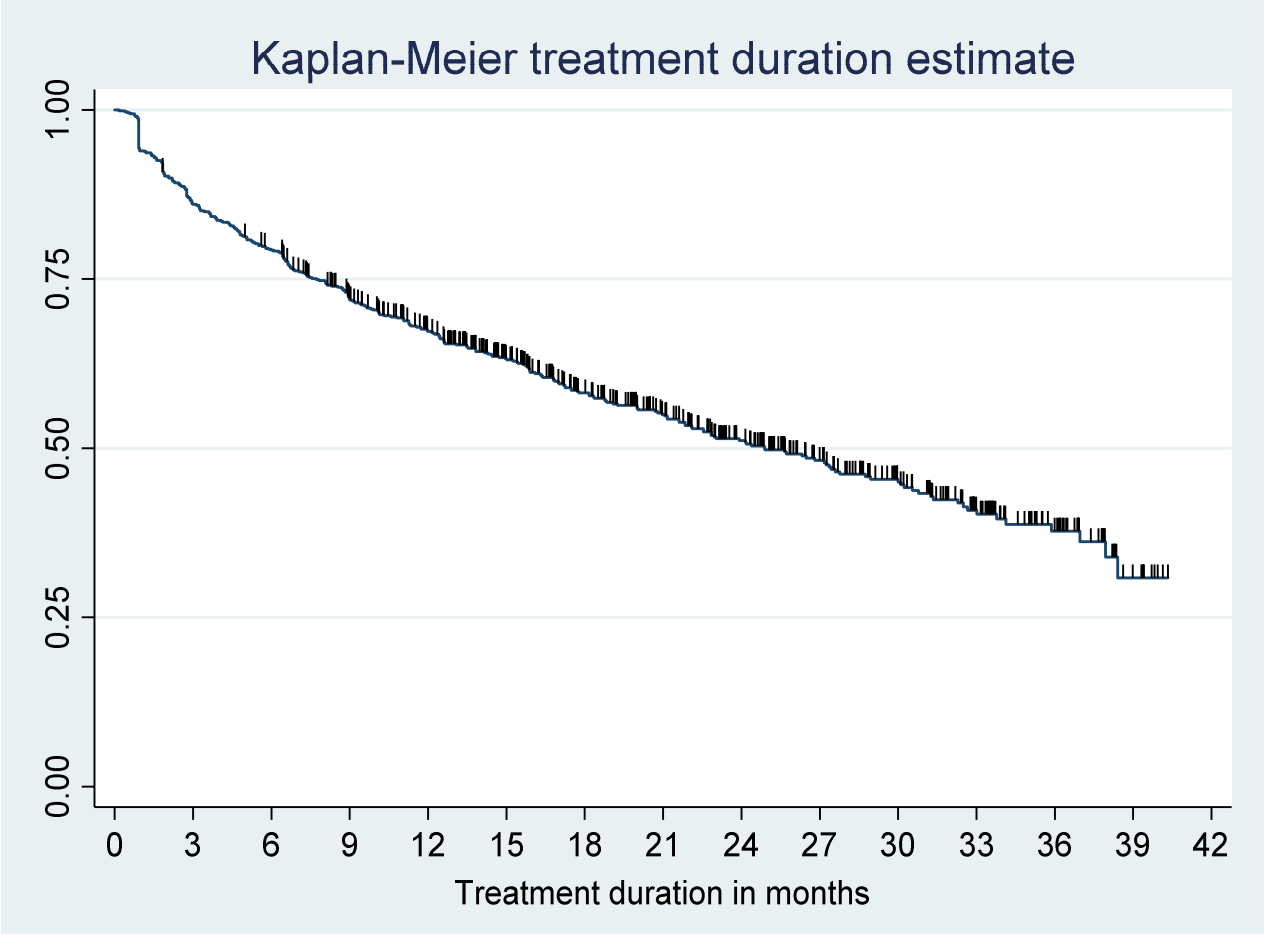


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 38 months (1,156 days).

Table 15. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Number at risk	724	622	570	499	434	356	291	241	194	146	110	71	36	8

Table 16 shows that for all patients who received treatment, 373 were still on treatment (censored) at the date of follow-up and 351 had ended treatment (events).

Table 16. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Censored	373	372	369	348	316	263	225	190	159	121	94	64	33	8
Events	351	250	201	151	118	93	66	51	35	25	16	7	3	0

Secondary sensitivity analyses

Mortality while on treatment

A secondary sensitivity analysis was carried out to calculate on treatment mortality. This method gives the death rate amongst patients who died on treatment, those who died in-between cycles and don't have an outcome of progression or toxicity.

CDF applications were limited from 28 September 2017 to 27 September 2020. All patients were traced for their vital status on 29 March 2021.

Censoring of patients

1. Patients who are still receiving treatment were censored at their final treatment date plus prescription length (28 days).
2. Patients who have ended treatment and are still alive were censored at their final treatment plus prescription length (28 days).
3. Patients who died not on treatment have been censored at their final treatment date plus prescription length (28 days).

Patients identified as a death on treatment are the event of interest and have been followed until their death date.

Patients have been censored if they:

- are still receiving treatment
- stopped treatment and are still alive
- stopped treatment - died not on treatment

Caveats will apply to the patient cohort who have been identified as a death on treatment. If for example, a patient dies in-between cycles and the trust has not confirmed the reason for stopping was progression/toxicity and so on.

823 patients were included in these analyses, of which, 770 were censored and 53 patients were identified as a death on treatment and the cohort of interest. The median follow-up time in SACT was 12.9 months (392 days).

Table 17. On treatment mortality at 6, 12, 18, 24 and 36 month intervals

Time period	On treatment OS (%)
6 months	96% [95% CI: 95%, 97%]
12 months	94% [95% CI: 92%, 96%]
18 months	93% [95% CI: 90%, 94%]
24 months	92% [95% CI: 89%, 94%]
36 months	87% [95% CI: 79%, 92%]

Figure 6 provides the Kaplan-Meier curve for on treatment mortality. The median survival was not reached.

Figure 6. Kaplan-Meier on treatment mortality plot (N=823)

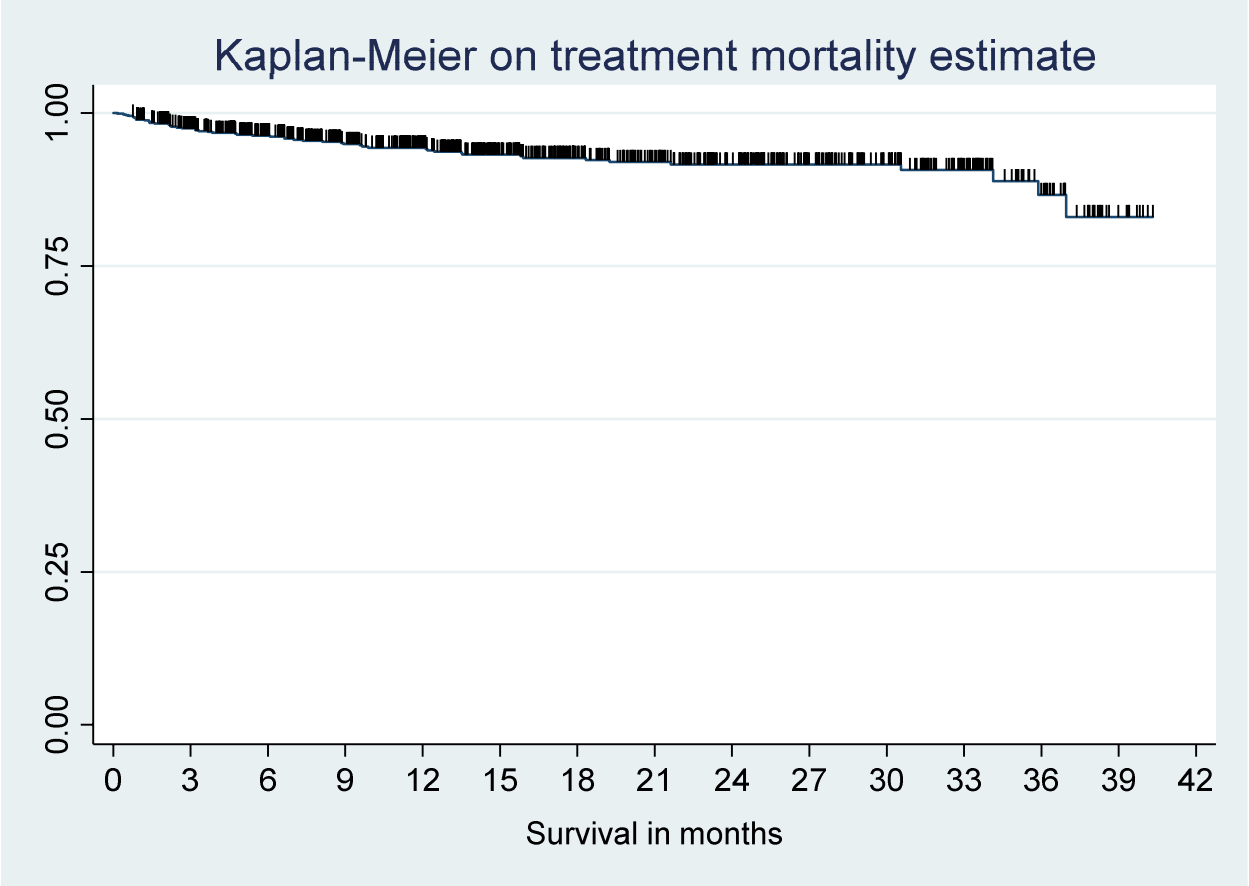


Table 18. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Number at risk	823	698	597	500	434	356	291	241	194	146	110	71	36	8

Table 19 shows that of the 53 patients identified as a death on treatment, the time in which events took place.

Table 19. Number of patients at risk, those that have died pre-progression (events) and those that have died not on treatment or still alive but treatment has ended (censored) by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Censored	770	665	572	483	420	347	284	236	190	142	106	68	35	8
Events	53	33	25	17	14	9	7	5	4	4	4	3	1	0

Treatment duration by prior lines

Sensitivity analysis was carried out by the Blueteq data item, prior lines. Two groups were included, 1 to 3 prior lines and more than 3 prior lines.

The median follow-up time in SACT, amongst those who received 1 to 3 prior lines was 13 months (395 days). The median follow-up time in SACT, amongst those who received more than 3 prior lines was 11 months (334 days)

Table 20. Treatment duration by prior lines at 6, 12, 18, 24 and 36 month intervals

Time period	1 to 3 prior lines treatment duration (%)	More than 3 prior lines treatment duration (%)
6 months	80% [95% CI: 77%, 82%]	75% [95% CI: 62%, 85%]
12 months	68% [95% CI: 65%, 72%]	56% [95% CI: 42%, 68%]
18 months	59% [95% CI: 55%, 63%]	
24 months	53% [95% CI: 48%, 57%]	35% [95% CI: 22%, 49%]
36 months	39% [95% CI: 33%, 45%]	26% [95% CI: 14%, 40%]

The Kaplan-Meier curve for ongoing treatment by prior lines is shown in figure 7. The median treatment duration amongst patients who received 1 to 3 prior lines of therapy was 26.5 months [95% CI: 22.1, 30.6] (806 days). The median treatment duration amongst patients who received more than 3 prior lines of therapy was 14.7 months [95% CI: 8.3, 23.0] (447 days).

Figure 7. Kaplan-Meier treatment duration by prior lines plot (N=823)

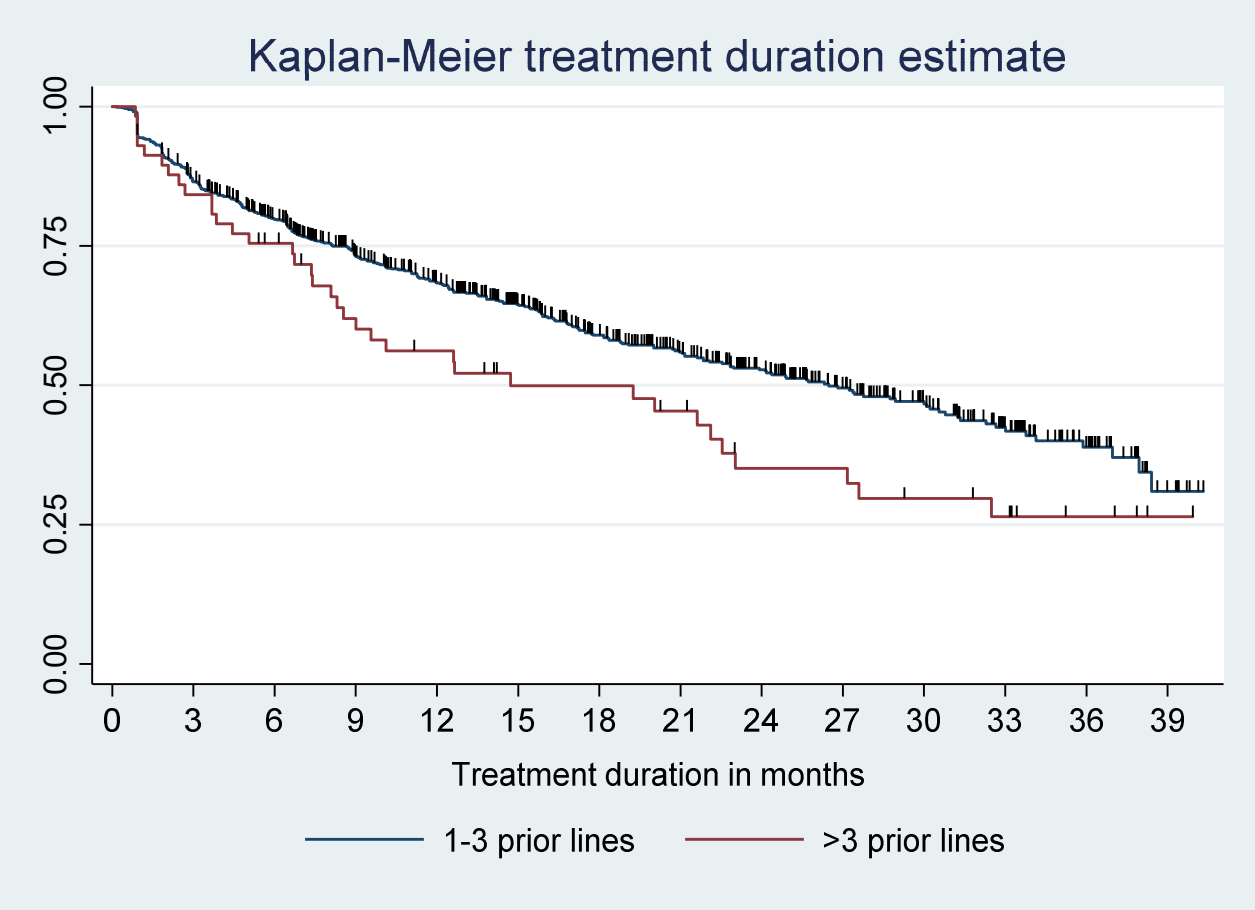


Table 21. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Number at risk: 1 to 3 prior lines	766	650	556	468	406	334	269	222	181	133	100	63	32	7
Number at risk: More than 3 prior lines	57	48	41	32	28	22	22	19	13	13	10	8	4	1

Table 22 shows that for all patients who received treatment and who received 1 to 3 prior lines, 434 were still on treatment (censored) at the date of follow-up and 332 had ended treatment (events).

Table 22. Number of patients at risk amongst patients who received 1 to 3 prior lines, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Censored	434	421	376	332	300	250	212	178	149	111	85	56	29	7
Events	332	229	180	136	106	84	57	44	32	22	15	7	3	0

Table 23 shows that for all patients who received treatment and who received more than 3 prior lines, 21 were still on treatment (censored) at the date of follow-up and 36 had ended treatment (events).

Table 23: Number of patients at risk amongst patients who received more than 3 prior lines, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-39	3-39	6-39	9-39	12-39	15-39	18-39	21-39	24-39	27-39	30-39	33-39	36-39	39
Censored	21	21	19	17	16	13	13	12	10	10	9	8	4	1
Events	36	27	22	15	12	9	9	7	3	3	1	0	0	0

OS by prior lines

Sensitivity analysis was carried out by the Blueteq data item, prior lines. Two groups were included, 1 to 3 prior lines and more than 3 prior lines. The median follow-up time in SACT amongst those who received 1 to 3 prior lines was 18.9 months (575 days). The median follow-up time in SACT amongst those who received more than 3 prior lines was 19.3 months (587 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 24. OS by prior lines at 6, 12, 18, 24 and 36 month intervals

Time period	1 to 3 prior lines treatment duration (%)	More than 3 prior lines treatment duration (%)
6 months	91% [95% CI: 89%, 93%]	
12 months	85% [95% CI: 82%, 87%]	
18 months	78% [95% CI: 75%, 81%]	
24 months	74% [95% CI: 70%, 77%]	60% [95% CI: 46%, 72%]
36 months	63% [95% CI: 58%, 68%]	37% [95% CI: 22%, 52%]

Figure 8 provides the Kaplan-Meier curve for OS by prior lines, censored at 29 March 2021. The median OS amongst patients who received 1 to 3 prior lines of therapy was not reached. The median OS amongst patients who received more than 3 prior lines of therapy was 28.5 months[m] (867 days).

[m] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Figure 8. Kaplan-Meier survival plot (N=823)

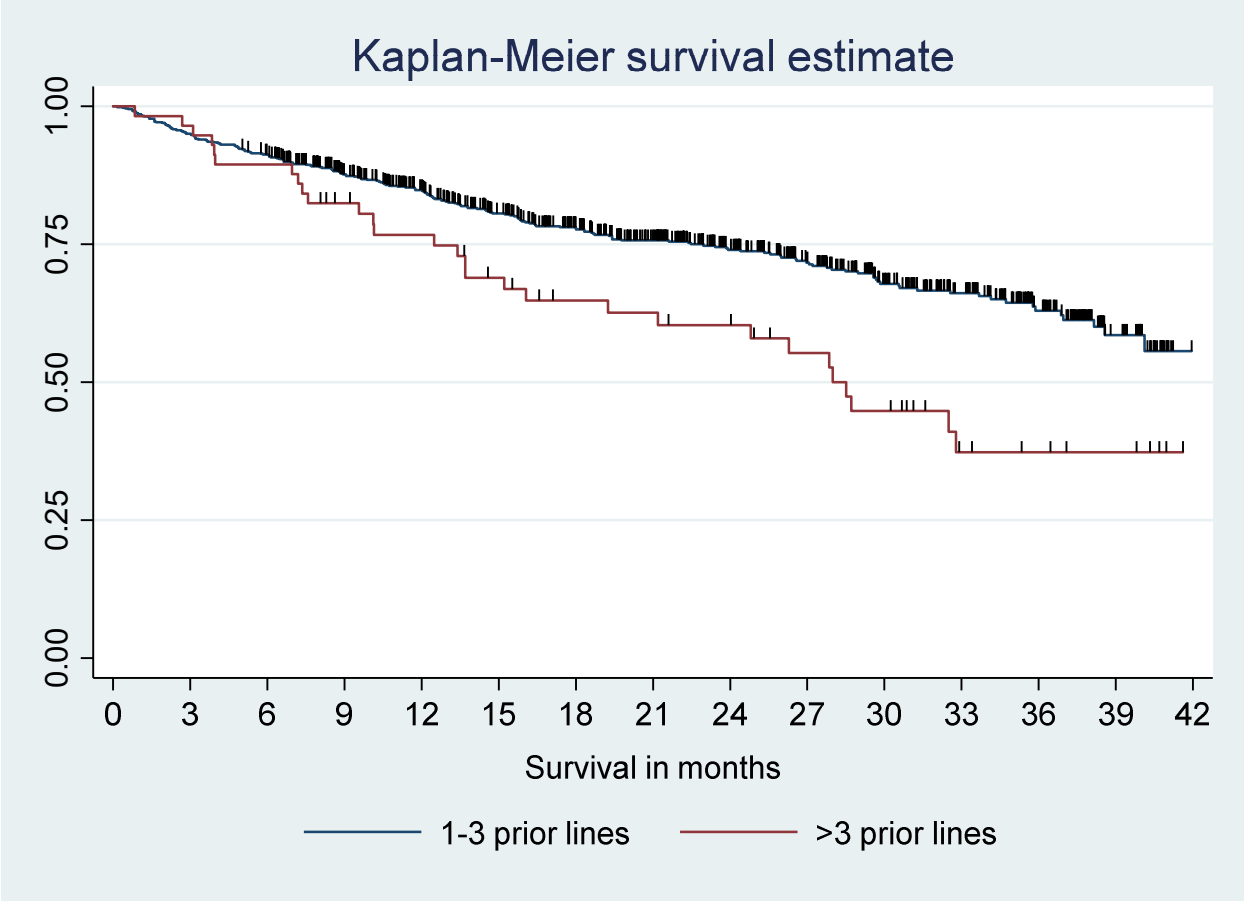


Table 25. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Number at risk: 1 to 3 prior lines	766	728	694	603	536	467	407	348	291	233	175	134	85	34
Number at risk: more than 3 prior lines	57	55	51	44	40	34	29	28	25	21	17	9	7	5

Table 26 shows that for all patients who received treatment and who received 1 to 3 prior lines, 562 were still alive (censored) at the date of follow-up and 204 had died (events).

Table 26. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints amongst patients who received 1 to 3 prior lines

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Censored	562	562	557	492	444	401	355	308	258	208	161	124	80	33
Events	204	166	137	111	92	66	52	40	33	25	14	10	5	1

Table 27 shows that for all patients who received treatment and who received more than 3 prior lines, 28 were still alive (censored) at the date of follow-up and 29 had died (events).

Table 27. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints amongst patients who received more than 3 prior lines

Time intervals (months)	0-42	3-42	6-42	9-42	12-42	15-42	18-42	21-42	24-42	27-42	30-42	33-42	36-42	39-42
Censored	28	28	28	25	24	22	19	19	17	15	15	9	7	5
Events	29	27	23	19	16	12	10	9	8	6	2	0	0	0

Table 28. Median treatment duration and OS, full cohort and sensitivity analyses

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Secondary sensitivity analysis: on treatment mortality	Third sensitivity analysis: 1 to 3 prior lines	Third sensitivity analysis: more than 3 prior lines
N	823	724	823	766	57
Median treatment duration	24.9 months [95% CI: 21.8, 28.9] (757 days)	24.9 months [95% CI: 21.6, 28.9] (757 days)		26.5 months [95% CI: 22.1, 30.6] (806 days)	14.7 months [95% CI: 8.3, 23.0] (447 days)
OS	Not reached			Not reached	28.5 months (867 days)
On treatment mortality			Not reached		

Conclusions

832 patients received ibrutinib for the treatment of Waldenström's macroglobulinaemia [TA491] through the CDF in the reporting period (28 September 2017 and 27 September 2020). 823 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. An additional 8 patients with a CDF application did not receive treatment and 19 patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 66% (N=544) of patients that received ibrutinib for Waldenström's macroglobulinaemia were male, 34% (N=279) of patients were female. Most of the cohort were aged 60 years and over (92%, N=758) and 71% (N=586) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 45% (N=368) of patients were identified as no longer being on treatment. Of these 368 patients, 19% (N=71) of patients stopped treatment due to progression, 13% (N=48) of patients stopped treatment due to acute toxicity, 7% (N=25) of patients chose to end their treatment, 27% (N=100) of patients died not on treatment, 14% (N=53) of patients died on treatment, 2% (N=8) of patients completed treatment as prescribed and 17% (N=63) of patients did not have a treatment record in SACT in at least 4 months and are assumed to have completed treatment.

Median treatment duration was 24.9 months [95% CI: 21.8, 28.9] (757 days). 79% of patients were still receiving treatment at 6 months [95% CI: 76%,82%], 67% of patients were still receiving treatment at 12 months [95% CI: 64%, 71%], 58% of patients were still receiving treatment at 18 months [95% CI: 54%, 62%], 51% of patients were still receiving treatment at 24 months [95% CI: 47%, 55%] and 38% of patients were still receiving treatment at 36 months [95% CI: 32%, 43%].

The median OS was not reached. OS at 6 months was 91% [95% CI: 89%, 93%], OS at 12 months was 84% [95% CI: 81%, 87%], OS at 18 months was 77% [95% CI: 74%, 80%], OS at 24 months was 73% [95% CI: 69%, 76%] and OS at 36 months was 61% [95% CI: 56%, 65%].

Sensitivity analysis was carried out on treatment duration to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for treatment duration showed no difference (full cohort = 24.9 months; sensitivity analysis cohort = 24.9 months).

A secondary sensitivity analysis was carried out to establish a death on treatment mortality rate. The median survival was not reached. OS at 6 months was 96% [95% CI: 95%, 97%]. OS at 12 months was 94% [95% CI: 92%, 96%], OS at 18 months was 93% [95% CI: 90%,

94%], OS at 24 months was 92% [95% CI: 89%, 94%] and OS at 36 months was 87% [95% CI: 79%, 92%].

A third sensitivity analysis was carried out on treatment duration and OS to evaluate outcomes by prior lines of therapy. Results for treatment duration showed a difference of 11.8 months between those who received 1 to 3 prior lines and those who received more than 3 prior lines (1 to 3 prior lines cohort = 26.5 months; more than 3 prior lines cohort = 14.7 months) although the difference was not statistically significant. The median OS was not reached amongst those who received 1 to 3 prior lines with the median OS being 28.5 months amongst those who received more than 3 prior lines.

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Appendix A

Previous treatment glossary

Previous treatment	Category
Bendamustine single agent	B mono
Bortezomib combination - rituximab	Bort R
Bendamustine plus rituximab	BR
Chlorambucil single agent	Cb mono
Chlorambucil plus rituximab	CbR
Cladribine plus rituximab	CladR
DRC	DRC
FCR	FCR
Other	Other
Rituximab single agent	R mono

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Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]

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None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Abdullah Pandor summarised and critiqued the clinical effectiveness data reported within the company's submission. Martin Orr critiqued the statistical aspects of the submission. Andrew Metry and Paul Tappenden critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

2L	Second-line
3L	Third-line
4L	Fourth-line
AE	Adverse event
AIC	Akaike Information Criterion
ASA	Additional sensitivity analysis
BIC	Bayesian Information Criterion
BR	Bendamustine plus rituximab
BSA	Body surface area
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CS	Company's submission
CSR	Clinical Study Report
DRC	Dexamethasone, rituximab and cyclophosphamide
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECR	European Chart Review
eMC	Electronic Medicines Compendium
eMIT	Electronic Market Information Tool
ERG	Evidence Review Group
ESS	Effective sample size
FCR	Fludarabine, rituximab and cyclophosphamide
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IgM	Immunoglobulin M
IIS	Investigator-initiated study
IPD	Individual patient data
IPSSWM	International Prognostic Scoring System for Waldenström's Macroglobulinemia
IV	Intravenous
IWWM	International Workshop on Waldenström's Macroglobulinemia
KM	Kaplan-Meier
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
mg	Milligram
MIMS	Monthly Index of Medical Specialities
ml	Millilitre
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
o.d.	Once daily
OS	Overall survival
PAS	Patient Access Scheme
PC	Physician's choice
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis

PSS	Personal Social Services
QALY	Quality-adjusted life year
R/R	Relapsed/refractory
RCT	Randomised controlled trial
RDI	Relative dose intensity
RMR	Rory Morrison Registry
RMST	Restricted mean survival time
SACT	Systemic Anti-Cancer Therapy
SmPC	Summary of Product Characteristics
SSE	Sum squared error
STC	Simulated treatment comparison
TA	Technology appraisal
TD	Treatment duration
ToE	Terms of Engagement
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
UK	United Kingdom
US	United States
WM	Waldenström's macroglobulinaemia
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.6. Background information on the original appraisal, the available evidence and information on non-key issues are in the main ERG report. All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

The key issues identified by the ERG are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID3778	Summary of issue	Report section
Issue 1	The evidence used to inform the company's CDF model remains highly uncertain	4.2
Issue 2	The company's model predictions of health state occupancy are not plausible	4.2

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the additional cost for every QALY gained.

Overall, the company's model suggests that ibrutinib affects QALYs by:

- Increasing the amount of time that patients with relapsed/refractory (R/R) Waldenström's macroglobulinaemia (WM) spend alive and progression-free compared with standard treatments.
- Increasing the amount of time that patients with R/R WM spend alive compared with standard treatments.

Overall, the company's model suggests that ibrutinib affects costs by:

- Increasing the costs associated with initial treatment for R/R WM, specifically due to the higher acquisition costs of ibrutinib compared with standard treatments.
- Reducing net treatment costs incurred following disease progression on initial therapy for R/R WM.

The modelling assumptions that have the greatest effect on the ICER are:

- The approach used to derive progression-free survival (PFS) for the ibrutinib-treated Systemic Anti-Cancer Therapy (SACT) population represented in the company's economic model
- The magnitude of the relative treatment effect on PFS for ibrutinib versus standard treatments.

1.3 Background and decision problem

This ERG report presents a summary and critique of the evidence submitted by the company to inform the Cancer Drugs Fund (CDF) guidance review of ibrutinib for treating R/R WM.

In November 2017, NICE published the following guidance recommendation: "*Ibrutinib is recommended, within its marketing authorisation, for use in the Cancer Drugs Fund as an option for treating Waldenström's macroglobulinaemia in adults who have had at least 1 prior therapy or as first-line treatment when chemo-immunotherapy is unsuitable, only if the conditions in the managed access agreement for ibrutinib are followed*." During the original NICE appraisal (Technology Appraisal Guidance Number 491 [TA491]), the key clinical evidence for ibrutinib was based on the 24-month results from Study 1118E - a single-arm open-label study undertaken in the United States (US). Data from Study 1118E were used to estimate PFS for the ibrutinib group of the company's economic model, and to estimate the relative treatment effect on PFS for ibrutinib versus physician's choice (PC) of standard therapy based on a multivariate Cox regression model comparing Study 1118E PFS data to that of a matched cohort from a European Chart Review (ECR). The data from Study 1118E were immature, which resulted in considerable uncertainty surrounding the magnitude of the relative treatment effect. The Appraisal Committee also noted concerns regarding uncertainty around pre-progression mortality (PPM) estimates used in the model. The Appraisal Committee concluded that more data were needed to address these clinical uncertainties, including data on overall survival (OS) from the SACT database, and updated efficacy data from Study 1118E and Arm C of the iNNOVATE trial (the ibrutinib monotherapy arm for patients with previously treated WM that is refractory to rituximab).

In July 2021, the company submitted additional evidence to inform the CDF guidance review for ibrutinib. The company's additional evidence includes a written submission (hereafter referred to as the "CDF-CS") which reports clinical data from multiple sources (see Section 1.4) and an updated health economic model which includes updated parameters informed by data from SACT and the Rory Morrison Registry (RMR), with additional data from Study 1118E included in scenario analyses. The CS and the company's clarification response indicate that the company's intention was to use the CDF model to reflect the SACT population in order to better represent English clinical practice. Despite the availability of additional clinical data collected during the period in which ibrutinib has been available

through the CDF, the company's indirect treatment comparison (ITC) has not been updated and the economic model retains the hazard ratio (HR) for PFS from the original model used to inform TA491.

1.4 Summary of clinical effectiveness evidence submitted by the company

The company submitted new evidence from four key data sources. This included updated clinical evidence with longer follow-up from Study 1118E (a single-arm, open label study which included 63 patients with WM who had received at least one prior therapy, with a median follow-up of 59 months), and iNNOVATE Arm C (a non-randomised sub-study of ibrutinib monotherapy which included 31 WM patients who were refractory to rituximab, with a median follow-up of 57.9 months). In addition, real-world evidence was also available from the SACT database (data on 823 patients with WM who had received at least one prior therapy before receiving ibrutinib in the NHS in England, with a median follow-up of 12.9 months [3-year final analysis]) and the UK-based RMR (data on 112 patients who had received or were receiving ibrutinib as a second- or subsequent-line treatment, with a median follow-up of [redacted]).

In general, despite differences in the baseline characteristics across the four data sources, WM patients in Study 1118E appeared to be younger (median age 63 years) and had less severe disease than WM patients in the SACT dataset (median age 75 years) who might routinely present in clinical practice in England. Median age was reported to be [redacted] for WM patients with prior therapy in the RMR cohort. In addition, the CDF-CS suggests that WM patients in the iNNOVATE study (median age 67 years), all of whom were refractory to rituximab, were more heavily pre-treated and were considered to have a poorer prognosis than those in Study 1118E and SACT. Naïve comparisons of Kaplan-Meier estimates across each data source indicated lower PFS probabilities in the RMR cohort than in Study 1118E and iNNOVATE Arm C. SACT does not collect data on disease progression and therefore no PFS data are available from this source. The CDF-CS suggests that variances in PFS may reflect differences in the definition and/or reporting of progression between clinical practice and trials.

OS data were available from all four data sources (Study 1118E, SACT, RMR and Arm C of iNNOVATE). Median OS was not reached in any data source. At 24 months, the proportion of patients still alive was 95% and [redacted] in Study 1118E and iNNOVATE arm C, respectively, versus [redacted] and 73% in the RMR and SACT datasets, respectively. Whilst lower OS probabilities were observed in the SACT and RMR cohorts compared with the prospective clinical studies (Study 1118E and iNNOVATE Arm C), the CDF-CS suggests that this may be a consequence of differences in the underlying baseline characteristics of patients between studies, for example, age at diagnosis (younger cohorts live longer than older cohorts).

The CDF-CS does not present any updated information regarding the relative effectiveness of ibrutinib versus standard treatments for WM.

The key issues relating to the clinical evidence for ibrutinib also impact on the company's updated cost-effectiveness analysis; hence, all key issues are presented together in Section 1.5.

1.5 Summary of cost-effectiveness evidence submitted by the company

The company's updated economic model is intended to reflect the SACT population of patients with R/R WM who have received at least one prior therapy. The company submitted an updated state transition model comprising five health states: progression-free on second-line (2L) therapy (either ibrutinib or PC); progression-free on third-line (3L) therapy; progression-free on fourth-line (4L) therapy; best supportive care (BSC), and dead.

The company's CDF base case model uses evidence from multiple sources, as follows:

- Ibrutinib group, time to treatment discontinuation (TTD) – exponential model fitted to data on treatment duration (TD) from SACT
- Ibrutinib group, PPM – based on the original estimate from the earlier data-cut of Study 1118E
- Ibrutinib group, PFS – an HR is estimated for TTD from SACT versus TTD from RMR which is then applied to the exponential model fitted to PFS data from RMR
- Ibrutinib group, OS – adjustment factor applied to post-progression mortality risks from ECR by calibrating modelled OS against OS data from SACT
- PC group, TTD – assumed to be equal to PFS for the PC group
- PC group, PPM – based on the original log-normal model fitted to data from the ECR
- PC group, PFS – estimated using the inverse of the HR from the company's original ITC applied to the PFS model for the ibrutinib group
- PC group, OS – modelled using the same post-progression mortality risks as the ibrutinib group.

In addition to the updated clinical parameters, the company also amended drug costs, updated some unit costs and resolved minor modelling errors identified by the ERG and the company. Additionally, the deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were amended to improve their functionality.

Based on a re-run of the probabilistic version of the company's CDF base case model by the ERG, ibrutinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained. The deterministic version of the model leads to a slightly lower ICER of [redacted] per QALY gained.

Issue 1: The evidence used to inform the company's CDF model remains highly uncertain

Report section	4.2
Description of issue and why the ERG has identified it as important	The company's CDF model uses evidence from multiple data sources as no single source provides information on all clinical inputs. Of particular importance, SACT does not collect PFS data, yet the company's economic model assumes that the treatment effect for ibrutinib versus PC is on PFS. For this reason, the company instead derived PFS for the SACT population using external data from RMR and assumptions (as described in the bullet points in Section 1.5). The ERG does not consider the company's approach for deriving PFS to be appropriate and notes that it leads to implausible model predictions (see Issue 2). In addition, the Terms of Engagement (ToE) for the CDF review state that *"the company should fully explore the most appropriate comparison based on data collected during the period of managed access, with particular focus on whether data from iNNOVATE can be used to establish the relative effectiveness of ibrutinib compared to standard of care."* This has not been done and the CDF model uses the HR obtained from the company's original ITC in TA491. The ERG believes that it would have been possible to undertake a population-adjusted ITC for PFS using the longer-term data from Study 1118E and the ECR. It is unclear whether a similar comparison could have been implemented using data from iNNOVATE Arm C. The ERG accepts that the data available to undertake further ITCs are subject to important limitations and that these may preclude the company from generating reliable estimates of relative treatment effects. However, the ERG considers that the company should still have attempted to perform these analyses and that these could have been explored in scenario analyses using the economic model. The ERG notes that although additional data have been collected during the period in which ibrutinib has been available through the CDF, these have not been used to reduce uncertainty around the relative clinical benefit of ibrutinib versus PC.
What alternative approach has the ERG suggested?	The ERG's preferred analysis re-estimates PFS for the ibrutinib group by assuming a proportional relationship between TTD and PFS in RMR and then applying this HR to the TTD model from SACT as a baseline. The analysis also uses the on-treatment mortality estimate for PPM and re-calibrates modelled OS to reflect the OS observed in SACT. The ERG believes that it would be possible to undertake a matching-adjusted indirect comparison (MAIC) using the longer-term data from Study 1118E and the ECR. This could be undertaken without reliance on the assumption of proportional hazards which would allow the longer-term data from Study 1118E to be taken into account.
What is the expected effect on the cost-effectiveness estimates?	The ERG's preferred analysis leads to a deterministic ICER of [redacted] per QALY gained for ibrutinib versus PC. This is higher than the company's base case ICER of [redacted] per QALY gained. The ERG's additional sensitivity analyses which apply less favourable HRs for PFS lead to higher ICERs.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that it is appropriate to re-focus the model population on the SACT cohort. However, there is considerable uncertainty around the health outcomes that would have been achieved in this population had they not received ibrutinib. The ERG believes that the company should attempt to undertake an updated ITC using the longer-term data from Study 1118E and the ECR. In addition, during the technical engagement stage, further expert opinion should be sought on expectations of PFS and OS for the PC group which could be used to assess the reliability of the HR for PFS obtained from the ITC and the plausibility of the model predictions.

Issue 2: The company's model predictions of health state occupancy are not plausible

Report section	4.2
Description of issue and why the ERG has identified it as important	The company's CDF model generates estimates of health state occupancy which are very different to those from the original TA491 model. The ERG has concerns that several of the CDF model predictions are not clinically plausible: (a) Ibrutinib group: The model suggests a large gap between TTD and PFS. This gap suggests that patients experience a mean lag of 1.18 years between the time at which they discontinue treatment with ibrutinib and the time at which they progress. The ERG's clinical advisor stated that patients are generally treated until progression and that those who discontinue before progression will progress after only a short period of time. (b) Ibrutinib group: The model suggests only a small gap between PFS and OS in the ibrutinib group. This suggests that patients treated with ibrutinib spend almost all of their survival time without disease progression. The ERG's clinical advisor did not consider this to be plausible and noted that patients who progress on ibrutinib are sometimes salvageable on 3L and 4L chemotherapy. (c) PC group: The model predicts that virtually all PC-treated patients (99.6%) will have died after around 6 years after starting initial treatment for R/R WM. The ERG's clinical advisor believed this was unrealistic as some patients survive beyond 6 years.
What alternative approach has the ERG suggested?	The ERG's preferred analysis which re-estimates PFS for the ibrutinib group: (i) reduces the gap between TTD and PFS; (ii) increases the gap between PFS and OS, and (iii) leads to higher estimates of OS for the PC group.
What is the expected effect on the cost-effectiveness estimates?	The ERG's preferred analysis leads to an ICER for [redacted] per QALY gained. The ERG's additional sensitivity analyses indicate that if the HR for PFS is assumed to be equal to 0.50, the ICER is increased to [redacted] per QALY gained. If the HR is assumed to be equal to 0.75, the ICER is increased to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	As discussed in Issue 1, further clinical input may be helpful to determine whether the HR for PFS is reliable and whether it leads to clinically plausible estimates of PFS and OS for the PC group.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The results of the ERG's exploratory analyses are summarised in Table 2. As shown in the table, the ERG's preferred analysis leads to an estimated ICER of [redacted] per QALY gained; this is higher than the company's deterministic base case ICER of [redacted] per QALY gained. If PFS is assumed to be equal to TTD (Additional Sensitivity Analysis [ASA] 1), the ICER is increased to [redacted] per QALY gained. The additional analyses in which the HR for PFS is reduced to 0.50 and 0.75 (ASA2 and ASA3) lead to higher ICERs of [redacted] and [redacted] per QALY gained, respectively.

Table 2: Summary of ERG preferred assumptions and ICERs

Scenario	Incremental QALYs	Incremental cost	ICER (change from company's updated base case)
Company's base case model	[redacted]	[redacted]	[redacted]
ERG-preferred analysis	[redacted]	[redacted]	[redacted]
ASA1 ERG preferred analysis plus PFS = TTD	[redacted]	[redacted]	[redacted]
ASA2 ERG preferred analysis plus treatment effect HR = 0.50	[redacted]	[redacted]	[redacted]
ASA3 ERG preferred analysis plus treatment effect HR = 0.75	[redacted]	[redacted]	[redacted]

ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group; ASA - additional sensitivity analysis; PFS - progression-free survival; TTD - time to treatment discontinuation; HR - hazard ratio; QALY – quality-adjusted life year

The ERG's full critique of the company's economic analyses and the ERG's exploratory analyses can be found in the main ERG report (Sections 4.2 and 4.3, respectively).

2. BACKGROUND

In June 2016, Janssen submitted evidence on the use of ibrutinib for treating relapsed/refractory (R/R) Waldenström's macroglobulinaemia (WM) to inform NICE Technology Appraisal (TA) Number 491.[1] The clinical effectiveness evidence and the cost-effectiveness model for ibrutinib were focussed on Study 1118E.[2] This is a single-arm, open-label study which included 63 patients with R/R WM who had received at least one line of prior therapy. At the time of the original appraisal, outcomes data from this study were available from 24 months of follow-up and median progression-free survival (PFS) and overall survival (OS) had not been reached. Long-term predictions of health outcomes for patients receiving ibrutinib relied on parametric survival models fitted to data from Study 1118E. The Final Appraisal Determination (FAD) for TA491 issued in September 2017 concluded that *"the longer-term effects on progression and survival are uncertain because no data are available."*[3]

The comparator considered in the company's submission (CS) for TA491 was referred to as "physician's choice" (PC) of standard therapy and was assumed to be comprised of a blend of alternative second-line rituximab/chemotherapy options, including: (i) bendamustine and rituximab (BR); (ii) dexamethasone, rituximab and cyclophosphamide (DRC); (iii) fludarabine, cyclophosphamide and rituximab (FCR); (iv) cladribine and rituximab; (v) cladribine monotherapy; (vi) rituximab monotherapy; (vii) chlorambucil and rituximab, and; (viii) chlorambucil monotherapy. As Study 1118E[2] did not include a comparator arm, the company estimated the relative effectiveness of ibrutinib versus PC using an indirect treatment comparison (ITC) based on data from Study 1118E and a retrospective observational study of outcomes for European patients receiving other treatments for WM (hereafter referred to as the European Chart Review [ECR]).[4] In order to undertake this ITC, the company matched a subset of patients from the ECR against patients from Study 1118E and fitted a multivariable Cox regression model to estimate the hazard ratio (HR) for PFS.[1] The Evidence Review Group (ERG) raised several concerns about this approach, and critiqued the methods used to select the matched cohort.[5] The Appraisal Committee concluded that *"there remains considerable uncertainty about the size of the long-term benefit because of limitations in the data available."*[3]

The company's economic analysis in TA491 was based on a cohort-level state transition model which estimated the incremental cost-effectiveness of ibrutinib versus PC from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. The model included five health states: (i) second-line (2L) progression-free; (ii) third-line (3L) progression-free; (iii) fourth-line (4L) progression-free; (iv) best supportive care (BSC) and (v) dead. As the model adopted a state transition approach, whereby OS is not modelled directly but is instead estimated as a function of all other transitions, the model required additional parameters to be estimated. In particular, in the Appraisal Committee's preferred model, pre-progression mortality (PPM), which relates to the risk of death before

progression, was estimated based on the three death events which occurred within the 24-month follow-up period of Study 1118E.[2] The limited evidence to inform this component of PFS was considered to be highly uncertain at the time of the original appraisal.

In addition, the ERG raised concerns regarding the interpretation and analysis of the risk of death within the ECR and highlighted several mismatches between the subsets of data from the ECR used to estimate event risks in the model, and the definition of those risks in the economic model. This further contributed to uncertainty in the results of the company's original model. A detailed critique of the company's original model and the uncertainties around the evidence used to inform it can be found in the original ERG report.[5]

According to the FAD for TA491,[3] the Appraisal Committee concluded that, taking into account the uncertainties identified, the most plausible incremental cost-effectiveness ratio (ICER) was likely to be at least £54,100 per quality-adjusted life year (QALY) gained, as estimated in the company's base case analysis. The committee agreed that ibrutinib did not meet NICE's End-of-Life (EoL) criteria because the first criterion of life expectancy being less than 24 months was not met. As such, the Appraisal Committee concluded that the ICER for ibrutinib was substantially higher than the range normally considered as a cost-effective use of NHS resources for technologies which do not meet the EoL criteria (£20,000 to £30,000 per QALY gained). The Appraisal Committee further concluded that it would be able to recommend ibrutinib as an option for use within the Cancer Drugs Fund (CDF) for treating WM provided that a Managed Access Agreement (MAA) was in place that allowed ibrutinib to be used cost-effectively within the CDF. Ibrutinib was subsequently accepted onto the CDF with an MAA [redacted] whilst more clinical data were collected from real-world databases and clinical studies.[3]

In May 2021, NICE issued a document which sets out the Terms of Engagement (ToE) for the CDF review of ibrutinib for treating WM.[6] The headline points regarding the Appraisal Committee's preferred assumptions and data sources included in the ToE for the CDF review are outlined in Table 3. In particular, the Systemic Anti-Cancer Therapy (SACT) database was identified as an appropriate data source for time to treatment discontinuation (TTD), OS, and PPM, and longer-term data were expected to be collected from Study 1118E and Arm C of the iNNOVATE trial.[6]

This ERG report presents a summary and critique of the additional clinical evidence and updated economic analyses presented within the company's CDF submission[7] (hereafter referred to as the "CDF-CS").

Table 3: Headline points from Terms of Engagement for CDF review

Issues	NICE Appraisal Committee position
Population	Adults with WM who have had at least 1 prior therapy are the relevant population for the CDF review.
Comparators	The company should present clinical and cost-effectiveness evidence for ibrutinib compared to the "physician's choice" comparator that was used for decision-making within the original appraisal.
Survival data	The company should use more mature PFS and OS data using data collected through SACT, Study 1118E, iNNOVATE and the WMUK (RMR) registry.
PPM	The company should use data collected through SACT, and more mature data from Study 1118E and iNNOVATE to inform pre-progression mortality. Time to progression rather than time to subsequent treatment should be used to calculate pre-progression mortality.
Comparative effectiveness	The company should fully explore the most appropriate comparison based on data collected during the period of managed access, with particular focus on whether data from iNNOVATE can be used to establish the relative effectiveness of ibrutinib compared to standard of care.

PFS - progression-free survival; OS - overall survival; SACT - Systemic Anti-Cancer Therapy; WMUK - Waldenström's macroglobulinaemia UK; RMR - Rory Morrison Registry; PPM - pre-progression mortality; WM - Waldenström's macroglobulinaemia

3. CLINICAL EFFECTIVENESS

This section summarises the additional clinical evidence for ibrutinib presented in the CDF-CS.[7]

3.1 Summary of clinical evidence for ibrutinib included in the CDF-CS

The original CS for TA491[1] included clinical evidence from two key sources: (i) a single-arm, open-label study (PCYC-1118E [Study 1118E]) which included 63 patients with WM who had received at least one prior therapy[2] and (ii) a non-randomised sub-study of ibrutinib monotherapy (iNNOVATE Arm C) which included 31 WM patients who were refractory to rituximab.[8] A detailed critique of these studies can be found in the original ERG report submitted to NICE in 2016.[5] For this CDF review, the CDF-CS and accompanying appendices[7, 9] provide updated clinical evidence which includes longer follow-up from these two studies (59 months and 57.9 months, respectively) and additional real-world evidence collected from the SACT database[10] and the national Rory Morrison Registry (RMR).[11]

The SACT database[10] is a population-based resource of mandatory SACT activity from all NHS England providers, based on electronic clinical data collection. It has been designed to understand patterns in SACT prescribing and treatment outcomes. During the 3-year data collection period, the SACT database collected data on 823 patients with WM who had received at least one prior therapy before receiving ibrutinib. The CDF-CS[7] provides limited details on the completeness and accuracy of the SACT dataset, especially with respect to clinical outcomes (CDF-CS, Appendix B.3[9]). Although SACT does not allow for the systematic tracking of clinical outcomes such as OS, PFS, response or remission,[12] the company's clarification response[13] (question B2) explains that TTD and OS were estimated based on the following data: start date of regimen and cycle; administration date, and the reason for stopping treatment. For the subgroup of patients that had ended treatment (n=368), data field completeness for the outcome summary of why treatment was stopped was 70%.[13] Despite the limitations of the SACT dataset, and the need to collect additional data either through new data fields in SACT or from other sources (e.g., electronic health records),[12] the ERG and their clinical advisor consider that the SACT dataset provides real-world data that are representative of clinical practice in the NHS in England.

The RMR was established in August 2017. The RMR is a clinical registry that collects data from existing and new patients with WM (and related conditions) in the UK. It aims to gain a clearer picture of the landscape of WM and its treatment in the UK, to understand how treatment of WM is evolving and its impact on patients. The CDF-CS[7] states that the registry has grown to over 500 patients with confirmed WM. Of these, 112 patients had received or were receiving ibrutinib as a second- or subsequent-line treatment (see CDF-CS,[1] page 15); this subset of patients is considered in the CDF-CS. Although the CDF-CS provides limited details regarding the completeness and accuracy of the RMR

dataset, CDF-CS Appendix B.2.2[9] states that data completeness rates by outcome (TTD, PFS, PPM and OS) for those patients who had received or were receiving ibrutinib as a second- or subsequent-line treatment were high ([redacted] for each individual outcome).

A brief summary of the study and population characteristics of the available evidence from Study 1118E,[14] iNNOVATE Arm C,[15] SACT[10] and RMR[11] is provided in Table 4. In general, despite differences in the baseline characteristics across the four studies, WM patients in Study 1118E appeared to be younger and had less severe disease than patients in the SACT dataset who might routinely present in clinical practice in England. Median age was reported for patients with prior therapy in the RMR cohort to be [redacted]; thus patients in RMR were, on average, older than Study 1118E patients. In addition, the CDF-CS[7] (page 26) suggests that WM patients in the iNNOVATE study, all of whom were refractory to rituximab, were more heavily pre-treated and were considered to have a poorer prognosis than those in Study 1118E and SACT.

Table 4: Summary of study and patient characteristics of updated and new evidence (adapted from CS, Table 3- 4 and Appendix B.3, Table 15)

	Updated evidence		New evidence	
Study title (acronym)	**PCYC-1118E[14]**	**PCYC-1127-CA (iNNOVATE)[15]**	**SACT[10]**	**RMR[11]**
Study characteristics				
Study design	Phase 2, single arm, open label trial	Phase 3 RCT with open-label sub-study (arm C)	Population-based observational study	Retrospective observational study
Location	USA	Multinational (Europe, USA, Oceania, and Canada)	England	England and Wales
Population	WM patients (≥18 years) with at least one prior line of therapy	WM patients (≥18 years) who were refractory to prior rituximab-containing therapy	WM patients with at least one prior line of therapy	WM patients (≥18 years) with at least one prior line of therapy (subgroup)
Intervention(s)	Ibrutinib mono (n=63)	Ibrutinib mono (n=31)	Ibrutinib mono (n=823)	Ibrutinib mono (n=112)
Comparator(s)	NA	NA	NA	NA
Outcomes collected that address committee's key uncertainties*	TTD; PFS; OS	TTD; PFS; OS; PPM	**TTD*; OS*;** OTM	**TTD*; PFS*;** OS; OTM; PPM
Follow-up (median)	59 months (final analyses)	57.9 months (final analyses)	12.9 months (3-year final analyses)	[redacted]
Baseline characteristics				
Male	48 (76%)	20 (65%)	544 (66%)	[redacted]
Female	15 (24%)	11 (35%)	279 (34%)	[redacted]
Age (median, years)	63 (range 44-86); (mean, 64.5)	67 (range 47-90)	75 (range NR)	[redacted]
Performance status				
≤1	63 (100%)	25 (81%)	469 (57%)	[redacted]
≥2	-	6 (19%)	132 (16%)	[redacted]
Missing	-	-	222 (27%)	[redacted]
IPSSWM risk at initiation				
Low	14 (22%)	7 (23%)	NR	[redacted]
Intermediate	27 (43%)	11 (35%)	NR	[redacted]
High	22 (35%)	13 (42%)	NR	[redacted]
Unknown	0	0	NR	[redacted]
Number of previous lines of treatments				
Median	2	4	NR	[redacted]
Range	1 to 9	2 to 6	NR	[redacted]

** Data sources shown in bold are used in the company's CDF base case model*

IPSSWM - International Prognostic Scoring System for Waldenström's macroglobulinaemia; NR - not reported; NA - not available; OS - overall survival; OTM - on-treatment mortality; PFS - progression-free survival; PPM - pre-progression mortality; RCT - randomised clinical trial; RMR - Rory Morrison Registry; SACT - Systemic Anti-Cancer Therapy; TTD - time to treatment discontinuation; mono - monotherapy

The key areas of clinical uncertainty discussed in the FAD for TA491[3] relate to the relative effectiveness of ibrutinib versus current treatments in terms of PFS and OS. The available data on PFS and OS from the four sources included in the CDF-CS[7] are summarised below. Other outcomes data for TTD and PPM are discussed in the context of the updated economic model in Section 4.

3.2 Progression-free survival

A summary of the available data on PFS from the studies is presented in the form of Kaplan-Meier plots in Figure 1. This includes updated data from Study 1118E[14] and iNNOVATE Arm C[15] as well as new evidence from the RMR dataset[11] (not previously presented). SACT does not collect data on disease progression and therefore no PFS data are available from this source; this is particularly important as the economic model is driven by treatment effects on PFS and the updated model is largely intended to reflect the SACT population (see Section 4). In general, higher rates of progression were observed in the RMR cohort than for patients in Study 1118E. The CDF-CS[7] (page 21) suggests that variances in PFS may reflect differences in the definition and/or reporting of progression between the clinical studies and NHS clinical practice (see Table 5). The ERG also notes that these plots do not include any adjustment for differences between patient characteristics across the studies; this may explain some of the apparent differences in PFS outcomes between the available sources.

Figure 1: Kaplan-Meier plots for PFS (RMR, Study 1118E, iNNOVATE Arm C; reproduced from CDF-CS, Figure 3)

1118E - Study 1118E; IRC - Independent Review Committee; RMR - Rory Morrison Registry; m - months

Table 5: Definition of PFS across data sources (adapted from CDF-CS Appendix B.4)

Data source	PFS definition
SACT	Not applicable
RMR	Biochemical PFS was defined as time from treatment start date to rise in serum IgM ≥ 25% or documented disease progression or death in months, expressed in Kaplan-Meier format
Study 1118E	PFS was defined as the time between the initiation of therapy and the date of disease progression, death, or last follow-up. The study protocol (available as supplementary material to Treon *et al.*[2]) defines progressive disease as *"a greater than 25% increase in serum IgM level occurs from the lowest attained response value or progression of clinically significant disease related symptom(s)."*
iNNOVATE (Arm C)	PFS, as assessed by IRC, is defined as the duration from the date of randomisation to the date of disease progression or death, whichever is first reported, assessed according to the modified VIth IWWM (NCCN 2014) criteria

SACT - Systemic Anti-Cancer Therapy; RMR - Rory Morrison Registry; IgM - Immunoglobulin M; IRC - Independent Review Committee; IWWM - International Workshop on Waldenström's macroglobulinemia; NCCN - National Comprehensive Cancer Network; PFS - progression-free survival

3.3 Overall survival

OS data were available from all four data sources: Study 1118E,[14] SACT,[10] RMR[11] and Arm C of iNNOVATE[15]. Median OS was not reached in any data source (see Table 8 of the CDF-CS[7] for additional details). Kaplan-Meier plots for OS from all four sources are presented in Figure 2. At 24 months, the proportion of patients still alive was 95% and [redacted] in Study 1118E and iNNOVATE Arm C, respectively, versus [redacted] and 73% in the RMR and SACT datasets, respectively. Whilst lower OS probabilities were observed in the SACT and RMR cohorts compared with the prospective clinical studies (Study 1118E and iNNOVATE arm C), the CDF-CS (pages 24 to 25) suggests that this may be a consequence of differences in the underlying baseline characteristics of patients between studies, for example, age at diagnosis (younger cohorts live longer than older cohorts). In addition, Bomsztyk *et al.*,[16] suggest that this may also be due to referral bias in patients referred to tertiary referral centres for clinical trials. The authors also note that there are a number of other factors which likely contribute to worse outcomes in the older population, such as increasing comorbidities, reduced drug tolerance, and the need for attenuated doses, and death from other causes.

Figure 2: Kaplan-Meier plots for OS (SACT, RMR, Study 1118E, iNNOVATE Arm C; reproduced from CDF-CS, Figure 4)

1118E - Study 1118E; RMR - Rory Morrison Registry; SACT - Systemic Anti-Cancer Therapy; m – month

3.4 Relative effectiveness of ibrutinib versus standard treatments for WM

The CDF-CS[7] does present any additional evidence relating to the relative effectiveness of ibrutinib versus standard treatments for WM. The company's ITC has not been updated as part of this CDF guidance review; the company's economic model applies the original HR for PFS of 0.25 (95% confidence interval [CI] 0.11 to 0.57).

4. COST-EFFECTIVENESS

This section describes the amendments applied within the company's CDF model and the resulting cost-effectiveness estimates for ibrutinib versus PC. This section also presents the ERG's critical appraisal of the updated model and the methods and results of additional exploratory analyses undertaken by the ERG.

4.1 Description of CDF model amendments and cost-effectiveness results

4.1.1 Scope of economic analysis and model structure

The scope and the structure of the company's CDF model are the same as the original model used to inform TA491.[3] The CDF-CS[7] includes some minor changes to the nomenclature used to describe the health states to better reflect the characteristics of the target population and positioning of ibrutinib within the WM treatment pathway (see CDF-CS Appendix B.1.6.,[9] Figure 2). These changes do not impact on the model results.

4.1.2 Overview of key model changes

The company's CDF base case model includes a number of amended model parameters, as well as other amendments which alter or improve the functionality of the executable model. The key model amendments relate to the inputs for TTD, PFS and OS (via PPM and post-progression mortality risks) in the ibrutinib group. The ERG notes that as a consequence of the company's modelling approach, the PFS and OS assumptions for the ibrutinib group also impact on the predicted health outcomes for the PC comparator group. In addition, the CDF model includes:

- Updated cost parameters (including drug acquisition and administration costs, resource use, adverse events [AEs] and terminal care costs)
- Updated general population life tables
- The correction of errors identified by the ERG during the original appraisal and additional minor errors subsequently identified by the company
- Updated functionality and specification of sensitivity analyses.

The CDF-CS[7] notes that the updated clinical inputs have the greatest impact on the estimated cost-effectiveness of ibrutinib and that the impact of other model amendments is minor.

4.1.3 Evidence used to inform the CDF model parameters

Table 6 summarises the updated evidence sources used to inform the parameters of the CDF base case model. The derivation of key parameters in the CDF base case model is discussed in more detail in the following sections.

Table 6: Comparison of evidence sources used to inform the original TA491 model and the CDF base case model

Parameter group	Parameter	TA491 model[1]	CDF base case model[1]
Patient characteristics	Mean age	Study 1118E[2]	SACT[10]
	Proportion male/female		
	Body surface area		Study 1118E[2]
Transition Probabilities	HR for PFS ibrutinib versus PC	Regression adjusted arm-based indirect comparison using Study 1118E[2] and the ECR[4] (multivariable Cox model, patients who had received ≤4 prior lines of therapy). Inverse HR for PFS from ITC applied to PFS model for ibrutinib to estimate PFS for PC.	Unchanged
	PFS – ibrutinib	Study 1118E[2]	HR estimated between TTD from SACT[10] and TTD in RMR[17] which is then applied to PFS from RMR
	PPM – ibrutinib	Age- and sex-adjusted life tables 2012-2014[18] (ERG preferred model included deaths observed in Study 1118E)	Estimated based on the 3 deaths reported in Study 1118E as published in 2015[2]
	PPM – PC	ECR[4] without censoring for progression events	ECR[4] considering only deaths during PFS
	Probability of progression – 3L and 4L treatment	ECR[4]	Unchanged
	PPS – 3L and 4L treatment and post-progression survival on BSC	ECR[4]	ECR[4] PPS probabilities multiplied by mortality adjustment factor derived by calibrating modelled OS against OS data from SACT[10]
	Probability patient progressing from 2L treatment receives 3L treatment	Expert opinion plus assumption[1]	Unchanged
	Probability patient progressing from 3L treatment receives 4L treatment	Expert opinion plus assumption[1]	Unchanged
TTD	TTD – ibrutinib	Assumed equal to PFS	SACT[10]
	TTD – PC		Assumed equal to PFS
AE frequency	Incidence of AEs due to 2L treatment	Study 1118E,[2] Tedeschi *et al*,[19] Tedeschi *et al*,[20] Dimopoulos *et al*,[21] Treon *et al*,[22] Electronic Medicines Compendium (eMC)[23]	AE frequencies for ibrutinib updated using later data-cut of Study 1118E.[14] AE frequencies for the PC group remain unchanged.

Parameter group	Parameter	TA491 model[1]	CDF base case model[1]
HRQoL	Utility - progression-free states	RESONATE trial[24]	Unchanged
	Utility - BSC	RESONATE trial,[24] Beusterien *et al*[25]	
	AE disutilities	Beusterien *et al*,[25] Tolley *et al*[26] and assumptions	
Resource use	Dosing regimen for ibrutinib	Ibrutinib SmPC[27]	Unchanged
	Dosing intensity for ibrutinib	Study 1118E CSR[28]	
	Dosing intensity for PC regimens	Assumed to be the same as ibrutinib	
	Dose and frequency of 2L PC regimens	Expert opinion plus assumption[1]	
	Dose and frequency of 3L and 4L treatments	Expert opinion plus assumption[1]	
	IV administration	Based on assumed dosing schedules	
	Follow up resource use	Expert opinion[1]	
	Hyperviscosity-related resource use	Expert opinion[1]	
Unit Costs	Drug acquisition	British National Formulary 2016[29]	MIMS 2020[30] and eMIT 2020[31]
	Drug administration	NHS Reference Costs 2014/2015[32]	NHS Reference Costs 2018/2019[33]
	Follow up		
	Hyperviscosity		
	Management of AEs		
	Terminal care	Round *et al*[34] inflated to 2015 prices	Round *et al*[34] inflated to 2019 prices

ECR - European Chart Review; 2L - second-line; 3L - third-line; 4L - fourth-line; AE - adverse event; IV - intravenous; BSC - best supportive care; CSR - Clinical Study Report; eMIT - electronic market information tool; ERG - Evidence Review Group; HR - hazard ratio; HRQoL - health-related quality of life; IV - intravenous; MIMS - Monthly Index of Medical Specialities; OS - overall survival; PC – physician's choice; PFS - progression-free survival; PPM - pre-progression mortality; PPS - post-progression survival; RMR - Rory Morrison Registry; SACT - Systemic Anti-Cancer Therapy; SmPC - Summary of Product Characteristics; TA - technology appraisal; TTD - time to treatment discontinuation

Patient characteristics

The CDF model includes updated parameters relating to initial patient age and the proportion of men and women; these have been amended to reflect the population included in the SACT dataset.[10] The updated model assumes that patients have a mean age of 75 years at model entry and 66% of patients are men. The company retained the previous estimate of body surface area (BSA) of 1.96m^2 from Study 1118E[2] because SACT does not include data on BSA.

Time to treatment discontinuation – ibrutinib

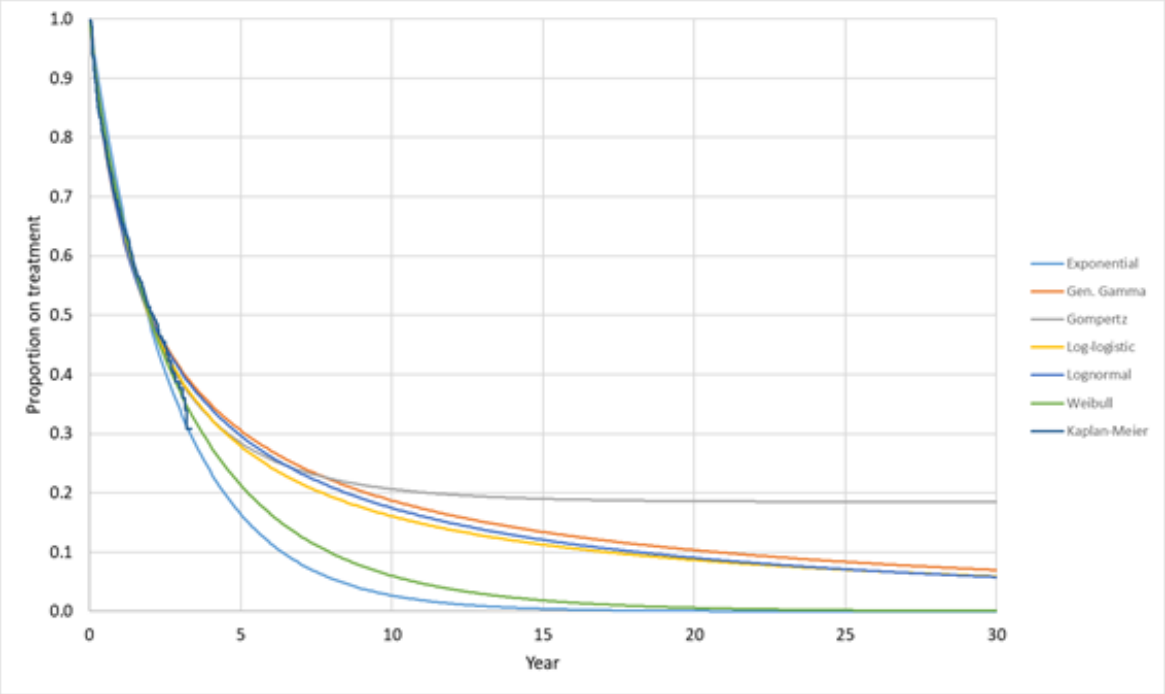
The TA491 model[1] assumed that TTD for ibrutinib was equivalent to PFS (i.e. patients are treated until disease progression); hence, TTD was not modelled separately to PFS. In contrast, the CDF model assumes that TTD and PFS are not equivalent. The CDF-CS[7] notes that *"over the course of the data collection period, it has become apparent that TD [treatment duration] is not a reasonable proxy for PFS. SACT data in combination with BlueTeq data, plus evidence from Study 1118E 5-year data-cut suggests that the relationship between TD and PFS is not equal."* (CDF-CS, page 7). Within the CDF model,[7] TTD for the ibrutinib group is modelled using a parametric survival model fitted to 3-year data on TTD from SACT,[10] whilst PFS is modelled using data from RMR and SACT (the derivation of PFS for the ibrutinib group is described later).

TTD for the ibrutinib group in the CDF model was based on data from the SACT report.[10] The company digitised the TTD data and generated pseudo individual patient data (IPD) using the method described by Guyot *et al*.[35] The company then fitted six standard parametric survival models to the available data; these included the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. The 2-parameter gamma model was not considered, nor were more flexible models. Model selection included consideration of the relative goodness-of-fit of the candidate models based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), as well as the visual fit and long-term plausibility of each model. The company's clarification response[13] (question B4) explains that the long-term plausibility of the candidate models was assessed via individual face-to-face video calls with four clinical experts in WM who were presented with the plot shown in Figure 3, as well as information about the percentage of patients who were still on treatment at different timepoints. Based on their experience, experts were asked to select the parametric survival model which seemed most clinically plausible. The CDF-CS[7] does not mention consideration of the empirical or modelled hazard to inform the selection of the preferred parametric model for TTD.

Figure 3 presents a comparison of the observed Kaplan-Meier survivor function from SACT[10] together with the predicted cumulative probabilities of TTD from the parametric survival models. AIC and BIC statistics are presented in Table 7. As shown in the table, the generalised gamma and log-normal models provided the best statistical fit according to the AIC and BIC, respectively. However, the company

stated that the resulting long-term extrapolations for these models were deemed to be clinically unrealistic. The company instead selected the exponential distribution for inclusion in the CDF base case model *"as the long-term projections were deemed to be closest to expected TD in clinical practice."*[7]

Figure 3: Kaplan-Meier plot and parametric survival models, TTD, SACT (reproduced from CDF-CS Appendix B.5, Figure 8)



Gen. gamma - generalised gamma

Table 7: AIC and BIC, TTD, SACT (adapted from CDF-CS Appendix B.5, Table 19)

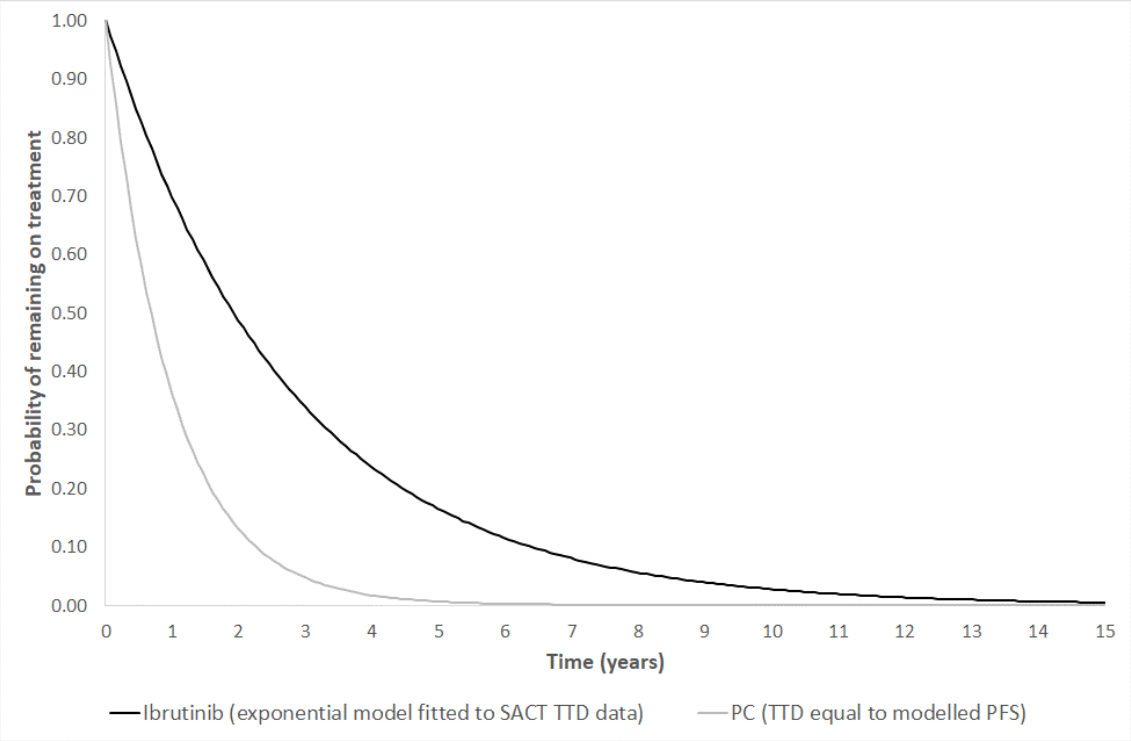
Model	AIC	BIC
Exponential	3325.43	3330.14
Weibull	3315.91	3325.34
Gompertz	3314.04	3323.46
Log-normal	3298.48	**3307.90**
Log-logistic	3311.00	3320.43
Generalised gamma	**3300.28**	3314.41

Bold indicates best-fitting model
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

For TTD in the PC group, the company retained the original assumption used in the TA491 model that patients will remain on treatment until progression.

The resulting TTD for each treatment group in the CDF model is shown in Figure 4.

Figure 4: Modelled TTD used in the CDF base case model (generated using the company's model)



SACT - Systemic Anti-Cancer Therapy; TTD - time to treatment discontinuation; PC – physician's choice; PFS - progression-free survival

Transition probabilities

A summary of the evidence used to inform the transition probabilities in the CDF model is summarised in Table 8. The transition probabilities in the updated model have been estimated using a variety of sources, including: PFS data derived from RMR for ibrutinib[11] (derived using the HR for TTD from SACT[10] and TTD from RMR[11]); PPM for ibrutinib from the earlier data-cut of Study 1118E;[14] the company's indirect comparison from the original CS for TA491;[1] PPM for PC and post-progression survival (PPS) in both groups from the ECR,[4] with the latter being multiplied by PPS adjustment factors derived by calibrating the model against OS data from SACT.[10]

Table 8: Evidence used to inform transition probabilities in the CDF base case model

Parameter	Ibrutinib	Physician's choice
2L PFS	HR of [redacted] estimated by comparing TTD in SACT versus TTD in RMR. This HR is applied to an exponential model fitted to PFS data from RMR to derive expected PFS in SACT	Estimated by applying the inverse of the HR for PFS of 0.25 from company's adjusted arm-based ITC to the ibrutinib derived PFS curve (matched cohorts between the earlier data-cut of Study 1118E for ibrutinib and the ECR for the PC group)*
2L PPM	Mortality rate estimated based on the three deaths occurring pre-progression in the earlier data-cut of Study 1118E (probability=0.0019 per cycle). This is in line with the ERG's preferred analysis in TA491	Log-normal model fitted to PPM data from ECR cohort for patients on 2L treatment*
3L and 4L TTP	Exponential distribution fitted to TTP data from the ECR cohort (patients starting 4L treatment, n=52, estimated probability = [redacted] per cycle)*	
3L and 4L PPM BSC death probability	Exponential distribution fitted to data from ECR cohort (patients progressed from 3L treatment, n=60, probability= [redacted] per cycle),* multiplied by an adjustment factor of 8.97 which was generated by calibrating OS in the economic model against OS observed in SACT	

** Indicates no change from the original TA491 model*
2L - second-line; 3L - third-line; 4L - fourth-line; BSC - best supportive care; HR - hazard ratio; RMR - Rory Morrison Registry; ECR - European Chart Review; OS - overall survival; PFS - progression-free survival; PPM - pre-progression mortality; SACT - Systemic Anti-Cancer Therapy; TA - technology appraisal; TTD - time to treatment discontinuation; TTP - time to progression

Progression-free survival – 2L treatment with ibrutinib

As discussed in Section 3.2, SACT does not collect data on PFS. However, PFS is a key endpoint within the company's economic model as the relative treatment effect for ibrutinib versus PC estimated from the ITC is applied to PFS. As such, the company had to estimate PFS using other external data. TTD was reported in both SACT[10] and RMR,[11] whereas PFS was only reported in RMR (see Table 4). The company's CDF base case model "derives" PFS for the SACT population by estimating an HR for TTD between RMR and SACT, and applies this HR to a model for PFS estimated using data from RMR. RMR was selected as the source for PFS as it reflects a subset of the SACT population.

The company digitised the PFS data from RMR[11] and generated pseudo-IPD using the method described by Guyot *et al*.[35] The company then fitted six standard parametric survival models to the available data; these included: the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. The 2-parameter gamma model was not considered, nor were more flexible models. Model selection included consideration of the relative statistical goodness-of-fit of the candidate models based on the AIC and the BIC, and the visual fit and long-term plausibility of the individual models. The company's clarification response[13] (question B5) states that judgements about plausibility were made by the company. The CDF-CS[7] does not mention consideration of the empirical or modelled hazard to inform the selection of the preferred model for PFS.

Figure 5 presents a comparison of the observed Kaplan-Meier survivor function for PFS (from RMR[11]) together with the predicted cumulative probabilities of PFS from the parametric survival models. AIC and BIC statistics are presented in Table 9. As shown in the table, the exponential model provided the best statistical fit according to both the AIC and BIC. The CDF-CS appendices[9] state that the Gompertz, generalised gamma, log-normal and log-logistic models were considered to be unrealistic as they suggest markedly higher probabilities of remaining alive and progression-free compared with the exponential and Weibull models. The company's clarification response[13] (question B5) further comments that given the age of patients at model entry (75 years), it is implausible that ≥10% of patients would still be alive and progression-free after 20 years. The company selected the exponential model for inclusion in the CDF base case model because it provided the best statistical fit to the data and for consistency with the parametric survival models selected for TTD and OS.

Figure 5: Kaplan-Meier plot and parametric survival models, PFS, RMR (reproduced from CDF-CS Appendix B.5, Figure 9)

Gen. gamma - generalised gamma; KM - Kaplan-Meier; PFS - progression-free survival; RMR - Rory Morrison Registry

Table 9: AIC and BIC, PFS, RMR (adapted from CDF-CS Appendix B.5, Table 19)

Model	AIC	BIC
Exponential	**281.25**	**283.9**
Weibull	283.22	288.52
Gompertz	282.84	288.15
Log-normal	281.72	287.02
Log-logistic	282.22	287.53
Generalised gamma	283.71	291.68

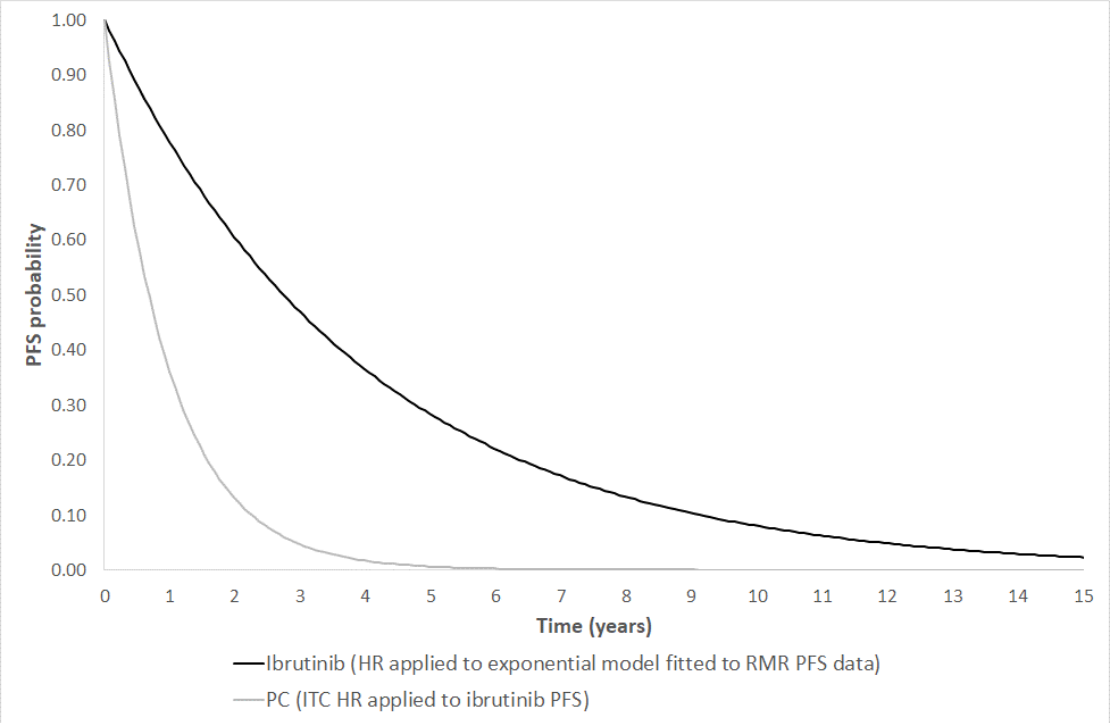
Bold indicates best-fitting model
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

In order to derive an expected PFS function for ibrutinib in the SACT population, the company estimated an HR between TTD observed in RMR[11] and TTD observed in SACT[10] by comparing restricted mean survival times (RMSTs) from each source. The HR estimated from this comparison was [redacted]. The company then assumed that the relationship between TTD across the studies is also transferable to PFS, and applied this HR to the exponential model fitted to data on PFS in RMR. The resulting derived PFS function is intended to reflect the PFS that would be expected in the SACT population if SACT collected data on progression. The company's clarification response[13] (question B4) states that the four clinical experts who provided judgements about the plausibility of the SACT TTD model were also asked to validate the derived PFS model. No details are provided regarding the output of the validation exercise or the means by which any potential concerns raised by individual experts, or disagreements between them, were addressed.

Progression-free survival – 2L treatment with PC

The CDF model uses the same approach to estimate PFS for the PC group as that used in the TA491 model.[1] As part of their original submission, the company undertook an ITC using a multivariable Cox model via matched data from Study 1118E[2] and the ECR.[4] As with the original TA491 model, the CDF model estimates PFS for the PC group by applying the inverse of the relative treatment effect estimate for PFS (HR = 0.25) to the parametric model for PFS for the ibrutinib group (derived from TTD data from SACT and RMR, and PFS from RMR, as described above).[1] Figure 6 presents the modelled PFS for the ibrutinib and PC groups in the CDF model.

Figure 6: Modelled PFS in CDF base case model (generated using the company's model)



HR - hazard ratio; ITC - indirect treatment comparison; PC - physician's choice; PFS - progression-free survival; RMR - Rory Morrison Registry

Pre-progression mortality – 2L treatment with ibrutinib

The evidence from SACT[10] and [redacted] suggests that approximately [redacted] of patients died whilst on treatment. The RMR data also indicate that approximately [redacted] of patients died prior to progression. The company did not have access to equivalent data on PPM from the 59-month data-cut of Study 1118E.[14] Arm C of the iNNOVATE trial included only 31 patients, of which only [redacted] died prior to progression ([redacted]).[15]

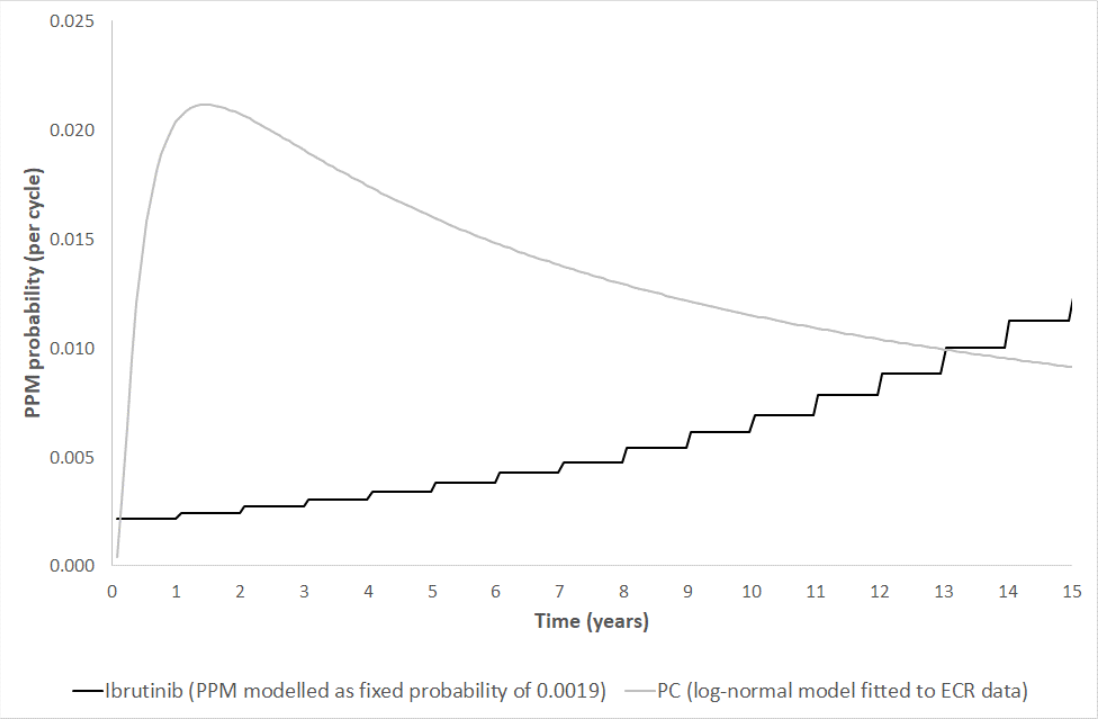
The company's CDF base case model retains the PPM probability applied in the ERG's exploratory analyses in TA491.[5] This PPM estimate was based on the earlier 24-month data-cut of Study 1118E, and was based on 3 death events (PPM probability per 28-day model cycle = 0.0019).[2]

Pre-progression mortality – 2L treatment with PC

PPM for the PC group was based on the same parametric survival model as that used in the original model in TA491.[1] The company used a log-normal survival distribution fitted to data on PPM for patients receiving second-, third- or fourth-line treatment in the ECR.[4]

Figure 7 summarises the per-cycle death probabilities for the ibrutinib and PC groups in the CDF base case model. PPM risks are capped by age- and sex-adjusted mortality risks for the general population based on UK life tables 2017-19,[36] thus mortality risks increase with age in both treatment groups. The ERG notes that in the CDF model, this cap has not been applied to PPM for the PC group beyond 13 years; however, this has a minimal impact as less than 0.0002% patients are expected to be alive and progression-free by this timepoint.

Figure 7: Modelled pre-progression death probabilities in the company's base case (generated using the company's model)

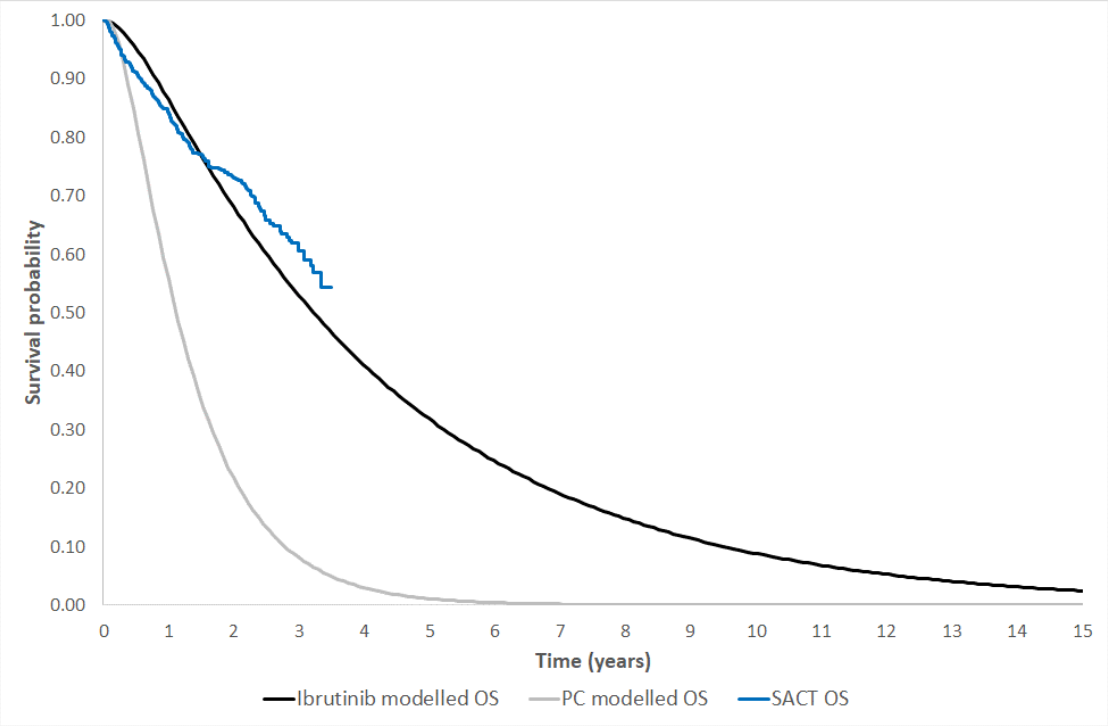


ECR - European chart review; PC - physician's choice; PPM - pre-progression mortality

Risk of death for 3L and 4L treatments and BSC (post-progression survival)

Whilst the SACT dataset[10] includes data on OS, the company's economic model does not use OS as a direct input; instead, mortality risk is modelled as a function of all transitions included in the model. The company incorporated the OS data from SACT[10] into the CDF model as a target data source against which post-progression mortality risks for downstream health states were calibrated (3L and 4L treatments and BSC, with PPS risks excluding adjustment obtained from the ECR[4]). The OS data from SACT were collected for a maximum of 3.36 years where the RMST was estimated to be 0.266 years compared to an RMST of 2.387 years in the ECR. Based on these data, the company calculated a mortality adjustment factor of 8.97 (2.387/0.266) and multiplied this by the previously estimated probability of death of [redacted] in the 3L, 4L and BSC states (derived from the ECR). Further details on the company's analysis of OS data from SACT are provided in CDF-CS Appendix B.5.3.[9] Figure 8 presents the modelled OS estimates from the CDF base case model. As with the modelled PFS function for ibrutinib, the company asked the four clinical experts who provided judgements about the plausibility of the SACT TTD survival distributions to also validate the modelled OS predictions. No details are provided regarding the output of the validation exercise or the means by which any potential concerns raised by individual experts, or disagreements between them, were addressed.

Figure 8: Modelled OS predictions in the company's base case versus observed OS in SACT (generated using the company's model)



OS - overall survival; PC - physician's choice; SACT - systemic anti-cancer therapy

Adverse event frequencies, disutilities and costs

The CDF model includes updated evidence on AE incidence with ibrutinib from the 59-month data-cut of Study 1118E.[14] Table 10 presents a comparison of the AE frequencies used in the original TA491 model alongside those used in the CDF model. The ERG notes that pneumonia is a new AE which was observed with the longer follow-up period in the study. AE frequencies for the PC group remain the same as those used in the original model.

The unit costs relating to the management of AEs were updated as per Table 3 of the CDF-CS appendices.[9] Table 11 summarises the once-only costs and utility decrements attributed to AEs from the company's CDF base case model and the original TA491 model.

Table 10: Adverse event frequencies associated with ibrutinib based on Study 1118E

AE	TA491 model (Study 1118E 24-month follow-up[2])	CDF model (Study 1118E 59-month follow-up[14])
Anaemia	1.6%	1.6%
Neutropenia	14.3%	17.5%
Thrombocytopenia	12.7%	11.1%
Infection (non-pneumonia)	6.3%	3.2%
Infection (pneumonia)	0%	3.2%
Diarrhoea	0%	0%

AE - adverse event

Table 11: Costs and utility decrements attributable to AEs for ibrutinib and PC regimens

Treatment regimen	Once-only costs attributed to management of AEs		Once-only utility decrements attributed to AEs	
	TA491 model	**CDF model**	**TA491 model**	**CDF model**
Ibrutinib	**£82**	**£134**	**-0.0021**	**-0.0023**
PC regimens:	**£91**	**£180**	**-0.0031**	**-0.0031**
• FCR	£153	£342	-0.0065	-0.0065
• DRC	£15	£33	-0.0006	-0.0006
• BR	£122	£247	-0.0041	-0.0041
• Cladribine + R	£110	£150	-0.0028	-0.0028
• Other treatment	£110	£150	-0.0028	-0.0028

AE - adverse event; TA - technology appraisal; CDF - Cancer Drugs Fund; PC - physician's choice; FCR; fludarabine, rituximab and cyclophosphamide; DRC - dexamethasone, rituximab and cyclophosphamide; BR - bendamustine plus rituximab; R - rituximab

Resource use and costs

The company's model includes updated estimates of the following resource costs:

- The company's model includes a confidential Patient Access Scheme (PAS) price discount for ibrutinib of [redacted] (resulting in a price of [redacted] per 140mg capsule).
- *Drug acquisition.* These were updated using estimates from the Monthly Index of Medical Specialities (MIMS) 2020 and the electronic Market Information Tool (eMIT) 2020.[30, 31] Table 1 and Table 5 of the CDF-CS appendices[9] summarise the updated drug costs used in the CDF base case model. The ERG notes that these have been updated to align with the ERG's recommendations in the critique of the original TA491 model.[5]
- *Drug administration.* The costs of intravenous (IV) drug administration for PC regimens, 3L, and 4L treatments were updated to reflect NHS Reference Costs 2018/2019[33] (an increase from £239.12 to £241.06). Table 12 summarises the drug acquisition and administration costs applied in the company's CDF base case model.
- *Routine follow-up costs.* These were corrected as per the ERG's recommendations (Table 60 of the ERG report[5]) and updated using NHS Reference Costs 2018/2019.[33] Table 13 presents the follow-up costs applied in the CDF model for patients in PFS either on 2L, 3L, or 4L treatments. A fixed cost of £51.06 was applied for all patients on BSC regardless of the health state duration.
- *Costs associated with unplanned medical resource use.* The cost of managing hyperviscosity was updated to £2,605.40 per event based on NHS Reference Costs 2018/2019.[33]
- *Terminal care costs.* The cost of cancer related death estimated from Round *et al.*[34] was inflated to £7,753 to reflect 2019 prices.

Table 12: Updated drug acquisition and administration costs applied in the CDF model

Regimen	Regimen component	Dose per administration	Treatment duration	Dose days per 28 days	Infusions per 28 days	RDI adjusted component cost per 28 days	RDI adjusted regimen cost per 28 days	RDI adjusted administration cost per 28 days
Ibrutinib	Ibrutinib (oral)	420mg o.d.	Until progression	28	0	[redacted]	[redacted]	£0
FCR	Fludarabine (IV)	25mg/m^2	6 x 28-day cycles	3	3	£119	£1,758	£224
	Cyclophosphamide (oral)	250mg/m^2		3	0	£15		
	Rituximab (IV)	375mg/m^2		1	1	£1,624		
DRC	Dexamethasone (IV)	20mg	6 x 21-day cycles	1.33	1.33	£13	£2,204	£598
	Rituximab (IV)	375mg/m^2		1.33	1.33	£2,165		
	Cyclophosphamide (oral)	100mg/m^2		6.67	0	£26		
BR	Bendamustine (IV)	90mg/m^2	6 x 28-day cycles	2	2	£142	£1,766	£673
	Rituximab (IV)	375mg/m^2		1	1	£1,624		
Cladribine+ rituximab	Cladribine (IV)	0.14mg/Kg	4 x 28-day cycles	5	5	£1,525	£3,149	£1,345
	Rituximab (IV)	375mg/m^2		1	1	£1,624		
Cladribine	Cladribine (IV)	0.14mg/Kg	4 x 28-day cycles	5	5	£1,525	£1,525	£1,121
Rituximab	Rituximab (IV)	375mg/m^2	4 x 7-day cycles	4	4	£6,496	£6,496	£897
Chlorambucil	Chlorambucil (oral)	0.2mg/Kg	6 x 28-day cycles	7	0	£89	£89	£0
Chlorambucil + rituximab	Rituximab (IV)	375mg/m^2	6 x 28-day cycles	1	1	£1,624	£1,713	£224
	Chlorambucil (oral)	0.2mg/Kg		7	0	£89		

FCR - fludarabine, rituximab and cyclophosphamide; DRC - dexamethasone, rituximab and cyclophosphamide; BR - bendamustine plus rituximab; o.d. - once daily; RDI - relative dose intensity; IV - intravenous

Table 13: Routine follow-up costs applied in the CDF model

Component	Annual resource use			Unit cost	NHS Reference Costs 2018/2019 code
	Years 1-2	Years 3-5	Year 6+		
Full blood count	5	4	3	£2.79	DAPS 05 Haematology
IgM	5	4	3	£6.53	DAPS 06 Immunology
Chemistry	5	4	3	£1.1	DAPS 04 Clinical biochemistry
Plasma viscosity	5	4	3	£6.53	DAPS 06 Immunology
Paraprotein	5	4	3	£1.1	DAPS 04 Clinical biochemistry
Haematologist	5	4	3	£166.51	*Haematology Service Code 303 [Total Cost]
Annual total cost	£922.80	£738.24	£553.68	-	-
Cost per cycle	**£70.74**	**£56.59**	**£42.45**	-	-

**Changed from the original submission TA491*
IgM – immunoglobulin M

4.1.4 Model evaluation methods

The CDF-CS[7] presents ICERs for ibrutinib versus PC generated using both the deterministic and probabilistic versions of the model. The results of the probabilistic sensitivity analysis (PSA) are presented as a cost-effectiveness plane, based on 1,000 Monte Carlo simulations. Cost-effectiveness acceptability curves (CEACs) are not presented in the CDF-CS, but are generated within the executable model. The results of the deterministic sensitivity analyses (DSAs) are presented as tornado plots, with the same results also presented in tabular form. The CDF-CS also reports the results of six additional scenario analyses which apply different distributions or which use alternative data sources for key model inputs for the ibrutinib group:

- Scenario analysis 1 – TTD from SACT modelled using a Weibull distribution (base case = exponential)
- Scenario 2 – HR for TTD from SACT and RMR estimated using truncated Kaplan-Meier functions (base case = full curves)
- Scenario 3 – PFS estimated using the later data-cut of Study 1118E (base case = RMR)
- Scenario 4 – PPM estimated using on-treatment mortality in SACT (base case = Study 1118E)
- Scenario 5 – PPM estimated using RMR (base case = Study 1118E)
- Scenario 6 – TTD and PFS estimated using later data-cut of Study 1118E (base case = SACT and RMR).

4.1.5 Cost-effectiveness results presented within the CDF-CS

Central estimates of cost-effectiveness

Table 14 presents the central estimates of cost-effectiveness for ibrutinib versus PC using the company's CDF base case model. Based on a re-run of the probabilistic version of the model by the ERG, ibrutinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained. The deterministic version of the model leads to a slightly lower ICER of [redacted] per QALY gained.

Table 14: Central estimates of cost-effectiveness

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic model[†]							
Ibrutinb	5.77	[redacted]	[redacted]	[redacted]	4.23	[redacted]	[redacted]
PC	1.53	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Ibrutinib	5.55	[redacted]	[redacted]	[redacted]	4.16	[redacted]	[redacted]
PC	1.39	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PC – physician's choice
** Undiscounted*
[†]*Generated from a re-run of the company's probabilistic model by the ERG*

Company's PSA results

Figure 9 presents CEACs for ibrutinib versus PC using the company's CDF base case model. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the company's model suggests that the probability that ibrutinib generates more net benefit than PC is [redacted] and [redacted], respectively.[redacted]

Figure 9: Cost-effectiveness acceptability curves (generated using the company's CDF model)

PC – physician's choice

Company's DSA results

Figure 10 presents the results of the company's DSAs in the form of a tornado plot. The company's DSAs indicate that the HR for PFS is a key driver of the ICER. The ICERs generated from the DSAs range from [redacted] per QALY gained (discount rate for health outcomes = 0%) to [redacted] per QALY gained (HR for PFS = [redacted] [upper limit of 95% CI]).

Figure 10: Deterministic sensitivity analysis (generated using the company's CDF model)

BSC - best supportive care; FU - follow-up; HR - hazard ratio; Ibr - ibrutinib; IV - intravenous; PC - physician's choice; PFS - progression-free survival; PPS - post-progression survival; RMR - Rory Morrison Registry; SACT - Systemic Anti-Cancer Therapy; SubTx1 - subsequent treatment line 1

Company's scenario analyses results

Table 15 presents the results of the company's scenario analyses. As shown in the table, the ICER for ibrutinib is moderately sensitive to the parametric distribution applied for TTD. The ICERs generated for the other scenarios are generally similar to the company's deterministic base case ICER. The lowest ICER was reported for the scenario in which PFS was derived from Study 1118E[14] rather than RMR (ICER = [redacted] per QALY gained).

Table 15: Company's scenario analysis results

Scenario no.	Scenario	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base case (deterministic)	4.16	[redacted]	[redacted]	[redacted]
1	SACT TTD distribution Weibull	3.68	[redacted]	[redacted]	[redacted]
2	Alternative HR for PFS from RMR	4.24	[redacted]	[redacted]	[redacted]
3	Ibrutinib trial-derived PFS from 59 month data-cut of Study 1118E	4.62	[redacted]	[redacted]	[redacted]
4	PPM for ibrutinib based on on-treatment mortality in SACT	4.13	[redacted]	[redacted]	[redacted]
5	PPM for ibrutinib based on RMR	3.96	[redacted]	[redacted]	[redacted]
6	Ibrutinib TTD and PFS taken from 59 month data-cut of Study 1118E	9.46	[redacted]	[redacted]	[redacted]

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SACT - Systemic Anti-Cancer Therapy; TTD - time to treatment discontinuation; HR - hazard ratio; PFS - progression-free survival; PPM - pre-progression mortality; RMR - Rory Morrison Registry
** Undiscounted*

4.2 ERG critique of the company's CDF model

4.2.1 CDF model verification

The ERG checked the programming of the updated CDF model, particularly with respect to how the new and updated evidence was incorporated into the executable model and how this flows through the logic of the model functions. The ERG identified two minor errors in the executable model:

(i) The total life years gained (LYGs) reported in the "Deterministic results" worksheet erroneously exclude PFS time following treatment discontinuation for the ibrutinib group. All results presented in this report include the correction of this error.

(ii) As described in Section 4.1.3, PPM in the PC group was not capped by general population mortality risks after 13 years.

Overall, the ERG believes that the amendments to the company's CDF model have been applied without error.

4.2.2 General issues relating to the use of data from multiple sources

The original model used to inform TA491 was hinged on outcomes data from Study 1118E,[2] the pivotal study of ibrutinib used to support the licensed indication for WM, and an indirect comparison of PFS between Study 1118E and a matched cohort from the ECR.[1, 4] With the exception of updated AE frequencies, the CDF base case model does not use any additional long-term clinical outcomes data from either of these two studies. Instead, the CDF model is centred around data for ibrutinib from SACT[10] (TTD and OS), with other data sources (RMR[11]) used to predict PFS, whilst health outcomes for the PC group are conditional on those for the ibrutinib group (modelled via the original HR for PFS from the ITC between Study 1118E and the ECR). The ERG has three general concerns regarding the company's approach to synthesising evidence from these sources.

Firstly, the CDF model reflects a very different population to that considered in the TA491 model and the health outcomes predicted by these two models differ considerably. As explained in the CDF-CS and the company's clarification response[13] (question B3), the company's intention was to use the model submitted for the CDF review to reflect the SACT population in order to better represent clinical practice in England. The ERG believes that this is a reasonable position to take, but notes that this differs from other NICE CDF guidance reviews in which the updated economic models typically address uncertainty through the inclusion of longer-term follow-up data from the same clinical studies used to inform the original model at CDF entry. As acknowledged by the company, the evidence available to implement the CDF model in the SACT population is not ideal. In particular: (a) none of the evidence sources provide head-to-head evidence of the relative effect of ibrutinib versus PC in any population, and (b) whilst the treatment effect for ibrutinib is modelled via its impact on PFS, SACT does not collect data on progression. Given the company's intention to centre the model around the SACT population, the absence of PFS data from this source means that the estimated incremental QALYs gains for ibrutinib versus PC using the company's model should be considered highly uncertain.

The second issue relates to the limited extent to which the CDF model reduces decision uncertainty. In TA491, the earlier data-cut of Study 1118E[2] included follow-up for PFS and OS up to a maximum of approximately 30 months. The TTD and OS data from SACT[10] are reported up to a maximum follow-up time of around 39 months. Whilst SACT reflects a more representative cohort of ibrutinib-treated NHS patients, the SACT OS data remain relatively immature and the maximum follow-up duration in SACT is not substantially longer than that in the earlier data-cut of Study 1118E. Longer-term PFS and OS data are available from Study 1118E; however, these have not been used to inform the CDF base case model because they reflect a different population.

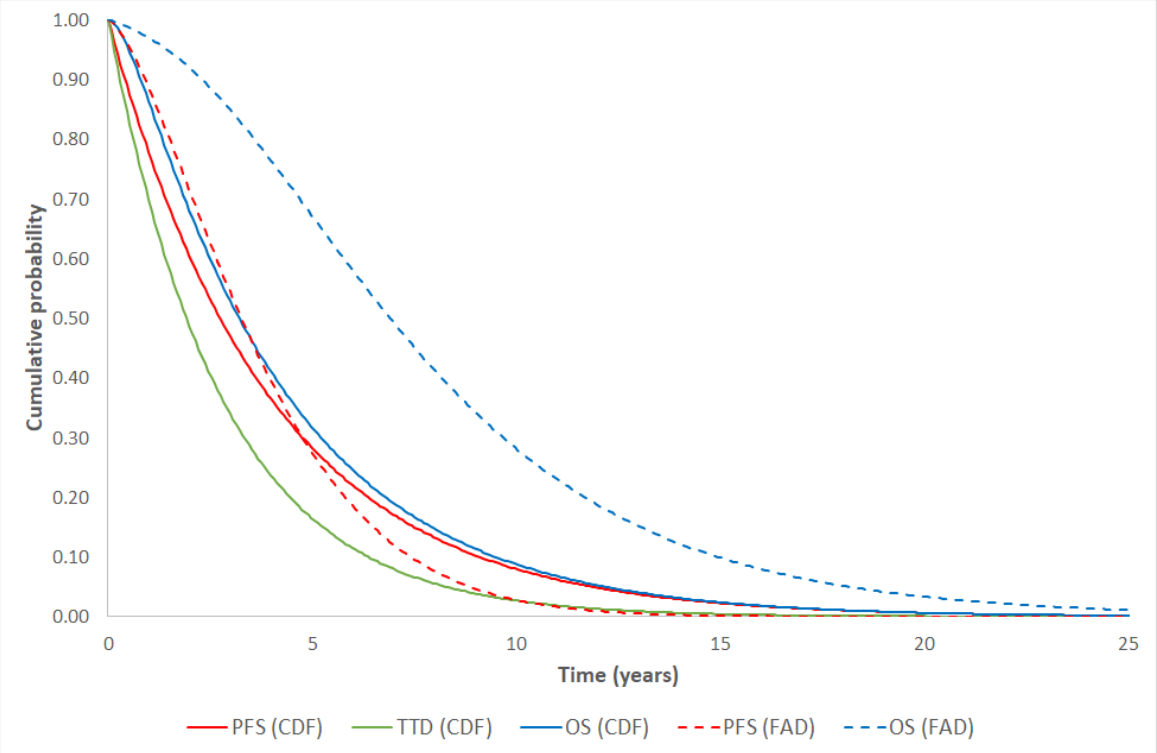
The third issue relates to the extent to which the CDF model adheres to the ToE for the CDF guidance review. The ToE document (Table 3) states that the company *"should use more mature, PFS and OS data using data collected through SACT, Study 1118E, iNNOVATE and the WMUK (RMR) Registry."*[6] The ERG notes that this condition has not been fully met because the CDF base case model does not use more mature data from Study 1118E[14] or Arm C of iNNOVATE[15] (although scenario analyses are presented using longer-term data from Study 1118E; see Table 15). However, it is unclear how the company could have used these additional evidence sources whilst also reflecting the WM population treated in the NHS. The ERG further notes that the company's choices regarding analytical approach were somewhat limited as Study 1118E is an investigator-initiated study (IIS) and the company did not have access to the IPD from the later data-cut.[9]

Overall, the ERG believes that the company's general approach of re-focussing the model around the SACT population is reasonable, but that the evidence available to estimate PFS for ibrutinib, and any outcome in the PC group, is subject to considerable uncertainty.

4.2.3 Concerns regarding plausibility of model predictions

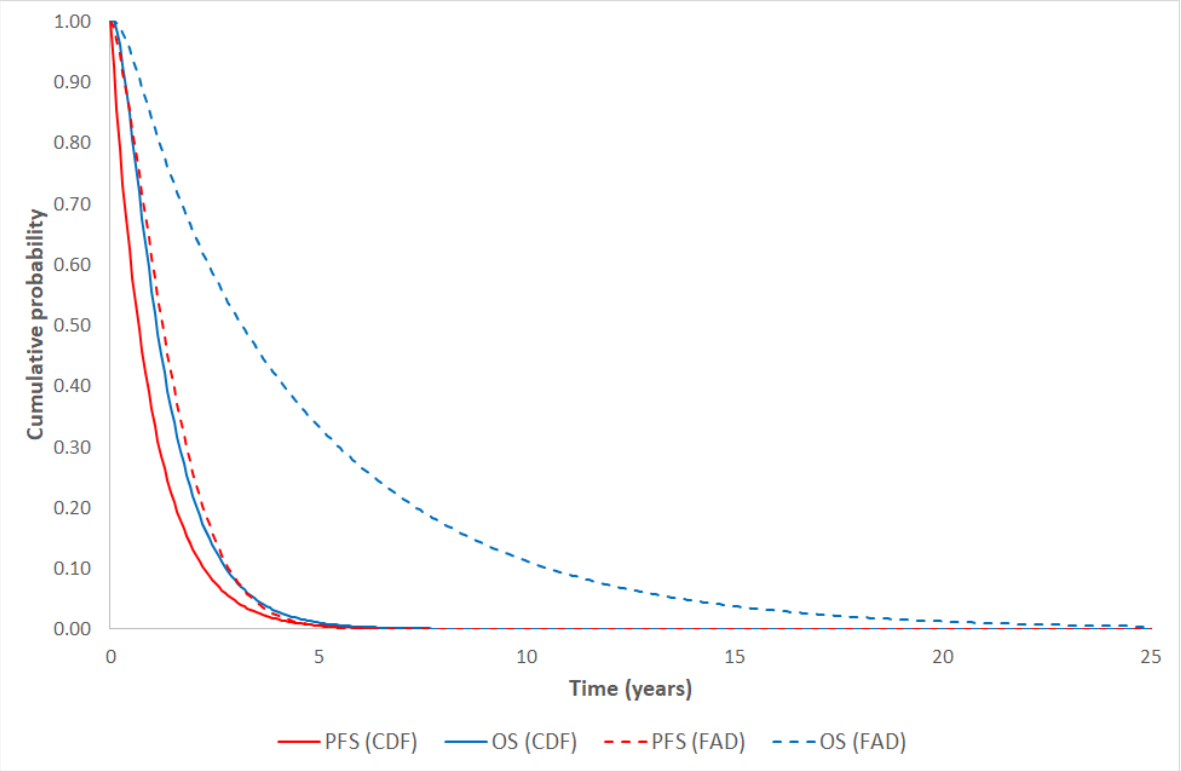
The ERG has concerns regarding the plausibility of the company's CDF model predictions and notes that these differ considerably from the predictions of the original TA491 model. Figure 11 and Figure 12 present comparisons of model-predicted TTD, PFS and OS from the original TA491 model (dashed lines) and the CDF model (solid lines) for the ibrutinib and PC groups, respectively. Table 16 summarises mean undiscounted times for TTD, PFS, PPS and OS for the ibrutinib and PC groups generated using the original TA491 FAD model and the CDF model.

Figure 11: Model-predicted TTD, PFS and OS from the TA491 FAD model and the CDF model, ibrutinib group (generated using the company's model)



PFS - progression-free survival; TTD - time to treatment discontinuation; OS - overall survival; CDF - Cancer Drugs Fund; FAD - Final Appraisal Determination

Figure 12: Model-predicted TTD, PFS and OS from the TA491 FAD model and the CDF model, PC group (generated using the company's model)



PFS - progression-free survival; OS - overall survival; CDF - Cancer Drugs Fund; FAD - Final Appraisal Determination
Note: TTD is assumed to be equal to PFS in the PC group

Table 16: Summary of mean undiscounted time in years for TTD, PFS, PPS and OS in the TA491 FAD model and the CDF model

Model-predicted outcome	TA491 model		CDF model	
	Ibrutinib	PC	Ibrutinib	PC
TTD	3.80	1.46	3.95	0.98
PFS	3.80	1.46	5.13	0.98
PPS	4.16	3.16	0.42	0.41
OS	7.96	4.62	5.55	1.39

TA - Technology Appraisal; FAD - Final Appraisal Determination; CDF - Cancer Drugs Fund; PC - physician's choice; TTD - time to treatment discontinuation; PFS - progression-free survival; PPS - post-progression survival; OS - overall survival

With respect to the predicted health outcomes for the ibrutinib group, the ERG notes the following observations:

- OS for the ibrutinib group is substantially lower in the CDF model compared with the original TA491 model (Figure 11, solid blue line versus dashed blue line). This difference is driven by the calibration of the model against the SACT OS data.[10]
- PFS for the ibrutinib group of the CDF model is greater than that in the TA491 model (Figure 11, solid red line versus dashed red line). Mean PFS in the TA491 model was 3.80 years compared with 5.13 years in the CDF model. This finding might be considered surprising given that the SACT population is 10.5 years older than the Study 1118E population, and because

CDF-CS Appendix B.3[9] (page 42) suggests that it is likely that the most severe WM patients may have initiated treatment with ibrutinib when it first became available on the CDF.

- The CDF model predicts a substantial difference between TTD and PFS (Figure 11, solid green line versus solid red line). The model predicts a mean lag of 1.18 years between the time at which patients discontinue treatment with ibrutinib and the time at which they progress. In the TA491 model, TTD was assumed to be equal to PFS (i.e. all patients were assumed to be treated until progression). The magnitude of the gap between the two curves is driven by the company's indirect approach used to estimate PFS for the ibrutinib group using data from SACT[10] and RMR[11] (see Section 4.1.3).
- The CDF model predicts only a small gap between PFS and OS (Figure 11, solid red line versus solid blue line). This indicates that the model predicts that patients spend almost all of their survival time in the progression-free state and that they die shortly after progression. The mean time spent in the post-2L states is much shorter in the CDF model than the TA491 model (mean PPS: TA491 model = 4.16 years; CDF model = 0.42 years).

With respect to the predicted health outcomes for the PC group, the ERG notes the following observations:

- OS for the PC group is substantially lower in the CDF model compared with the original TA491 model (Figure 12, solid blue line versus dashed blue line). The original TA491 model predicted a mean OS of 4.62 years, whereas the CDF model predicts a mean OS of 1.39 years. This difference is a consequence of the inclusion of new data to inform outcomes for the ibrutinib group and the company's modelling approach, rather than the availability of new data for the PC group.
- PFS is lower in the CDF model compared with the TA491 model (Figure 12, solid red line versus dashed red line). Mean PFS in the TA491 model was 1.46 years; mean PFS in the CDF model is 0.98 years.
- The CDF model predicts a small gap between PFS and OS (Figure 12, solid red line versus solid blue line). This indicates that patients spend most of their survival time in the progression-free state and die shortly after progression. Mean PPS after progressing on initial therapy in the CDF model is predicted to be 0.41 years. In contrast, the TA491 model predicted that patients spend 3.16 years alive following disease progression on initial therapy.

Section 4.2.4 provides a detailed critique of each amended CDF model input with reference to these model predictions.

4.2.4 Critique of amendments to clinical inputs

Clinical inputs - TTD for ibrutinib

The company modelled TTD for the ibrutinib group of the CDF model using an exponential model fitted to the TTD data from SACT.[10] The ERG notes the following issues regarding the company's approach:

- Given the company's objective of better reflecting NHS clinical practice in the CDF model, the ERG believes that the use of data on TTD from SACT[10] is appropriate.
- The exponential model was selected on the basis of clinical plausibility; however, this is the worst-fitting model according to the AIC and BIC (see Table 7). Compared with the other candidate survival models, the exponential distribution leads to patients spending the least amount of time on treatment, which in turn, leads to lower drug acquisition costs for ibrutinib.
- Whilst the description of the process used to select a preferred model for TTD in the CDF-CS and its appendices[7, 9] is limited, further information is provided in the company's clarification response[13] (question B4). The company's response indicates that clinical experts were shown plots of the full range of candidate survival models (Figure 3) and were asked to select their preferred model. The ERG believes it may have been better to elicit the clinicians' expectations of TTD at different timepoints, and to determine whether any of the fitted survival models are consistent with those expectations, rather than to select a preferred model directly, as it may be the case that none of the models considered are consistent with the clinicians' prior beliefs. As discussed in Section 4.1.3, the company does not appear to have included any consideration of the empirical or modelled hazard for TTD when selecting their preferred candidate survival distribution.
- As discussed in Section 4.2.3, the CDF model suggests a marked difference between modelled TTD and PFS (Figure 11, solid green line versus solid red line). The ERG's clinical advisor stated that patients usually stay on treatment until the point of progression, and that those who discontinue before that point progress soon after treatment is stopped. The company's clarification response indicates that the four clinical experts who provided judgements about preferred TTD models were also shown the model-predicted PFS functions for both treatment groups; however, it is unclear whether they were aware of the difference between modelled TTD and PFS in the ibrutinib group, or whether they would have considered this to be clinically plausible. This issue is discussed further below.

Clinical inputs - PFS for ibrutinib

The company's model assumes that ibrutinib impacts on PFS. However, PFS data are not collected in SACT[10] and so this source could not be used to inform the CDF model. Instead, the company indirectly estimated PFS in the SACT population by estimating an HR between TTD in SACT[10] and TTD in

RMR[11] and then applied this HR to a parametric survival model fitted to PFS data from RMR. Figure 13 presents Kaplan-Meier plots for TTD and PFS from RMR, exponential survival models fitted to the RMR data by the company (dashed green and red lines), as well as the TTD and derived PFS functions applied in the ibrutinib group of the CDF model (solid green and red lines).

Figure 13: Kaplan-Meier plots and fitted exponential models for TTD and PFS from RMR alongside TTD and PFS in the CDF model, ibrutinib group (generated using the company's model)

PFS - progression-free survival; TTD - time to treatment discontinuation; OS - overall survival; CDF - Cancer Drugs Fund; KM - Kaplan-Meier; RMR - Rory Morrison Registry

With respect to the company's approach to modelling PFS, the ERG notes the following:

- Given the company's objective of better reflecting NHS clinical practice in the CDF model, the absence of PFS data from SACT[10] represents a substantial problem for the economic analysis.
- The ERG's clinical advisor commented that the RMR[11] population is not representative of the SACT population as it is not as geographically dispersed and a small number of larger centres predominate.
- As discussed in Section 4.2.3, the CDF model predicts that ibrutinib-treated patients remain alive and progression-free for almost all of their remaining lifetime (Figure 11, solid red and solid blue lines). The ERG's clinical advisor did not consider this projection to be plausible and noted that patients who progress on ibrutinib are sometimes salvageable with 3L and 4L chemotherapy.
- The ERG believes that the company's approach to indirectly derive PFS for the SACT population is flawed and leads to inconsistent and implausible model predictions:

- As shown in Figure 13, there is only a small gap between the Kaplan-Meier functions for TTD and PFS from RMR[11] and the functions cross at several timepoints. This suggests either: clinicians continue to use ibrutinib beyond disease progression; that the PFS and TTD data from RMR are not based on the same group of patients, and/or that the underlying data are subject to some other problem(s) relating to data collection or analysis.
- The exponential models fitted by the company to the TTD and PFS data from RMR[11] (Figure 13, dashed green line and dashed red line) suggest only a small gap, which indicates that patients progress shortly after discontinuing ibrutinib.
- The TTD and PFS functions used in the CDF base case model (Figure 13, solid green line and solid red line) indicate a much larger gap, which suggests that patients spend a comparatively longer period of time progression-free following discontinuation of ibrutinib. Given that TTD in SACT[10] is lower than TTD in RMR[11] (see CDF-CS,[1] Figure 1) the ERG believes that this ought to imply that the gap between TTD and PFS in SACT should be less than that in RMR. However, the company's approach suggests the opposite.
- Given the limited evidence available, the ERG believes that it would be more appropriate to estimate the HR between the exponential models for TTD versus PFS in the RMR dataset[11] (estimated HR=[redacted]), and then to apply this HR to the TTD function from SACT[10] as a baseline. This approach rests on the assumption that the hazards for TTD versus PFS in RMR are proportional and that this relationship can be transported to other WM populations (e.g. SACT).

Clinical inputs - PPM for ibrutinib

The company's CDF base case model retains the PPM estimate from the earlier data-cut of Study 1118E.[2] This appears to be because SACT[10] does not report PFS and therefore this parameter cannot be estimated from this source (although data relating to on-treatment deaths are available from this source). The ERG notes the following:

- Given that on-treatment deaths in SACT must represent a lower bound for PPM (as discontinuation precedes progression), the ERG considers that it would be more consistent with the overall intended population of the model to estimate PPM using the data for on-treatment deaths from SACT,[10] acknowledging that this is an underestimate.
- The ERG's clinical advisor commented that PPM risk in the SACT population would undoubtedly be higher than that observed in Study 1118E,[14] primarily because of the differences in age across the populations leading to a higher risk of other-cause mortality.

Clinical inputs - OS for ibrutinib

OS data are available from the SACT dataset.[10] However, because the model uses a state transition approach, these data cannot be used directly as model inputs. Instead, the company calibrated the PPS risk estimated from the ECR[2] in both groups such that the model predicts OS for the ibrutinib group which is consistent with the SACT OS data. The ERG notes the following:

- Given the company's objective of better reflecting NHS clinical practice in the CDF model, the company's decision to indirectly use data on OS from SACT[10] is reasonable, although the approach used to estimate the PPS multiplication factor (described in CDF-CS[7] Section A.8.4) is somewhat unnecessary. The ERG believes that a simpler approach would be to minimise the sum squared error (SSE) between the observed Kaplan-Meier OS function from SACT and the model-predicted OS from the model trace.
- The ERG believes that the adequacy of the company's calibration approach is reliant on all other event risks in the ibrutinib group (i.e. PFS and PPM) being correctly specified. As shown in Figure 8, the modelled OS function does not provide a very good representation of the observed data from SACT and the model underestimates OS after around 1.7 years. This may indicate that one or more of the model inputs is poorly specified.

Clinical inputs for PC (PFS, PPM and PPS)

Most clinical input parameters for the PC group in the CDF model remain the same as those used in the TA491 model.[1] However, as shown in Figure 11 and Figure 12, predicted OS in the CDF model is very different to that from the original TA491 model. This is largely because PPS is modelled using the higher mortality risks obtained from the company's calibration approach. The ERG notes the following concerns:

- Whilst the ERG agrees that it is reasonable to expect different outcomes for PC in a SACT-type population, there are no new data to inform health outcomes for the PC comparator group – the CDF model predictions for the PC group are an artefact of the company's modelling approach, rather than the availability of new evidence for PC.
- The PPS risk for PC is based on the calibrated probabilities for the ibrutinib group. In the absence of other data, it is unclear what else the company could have done, but this aspect of the model should be considered highly uncertain.
- The ERG's clinical advisor commented that the CDF model predictions of OS for the PC group are not plausible, as the model suggests that virtually all PC-treated patients (99.6%) will have died after around 6 years (see Figure 12, solid blue line). The clinical advisor suggested this represents an overestimate of mortality risk for PC-treated patients.
- The ITC performed in TA491 has not been updated; hence, the CDF-CS[7] does not provide any additional evidence to reduce uncertainty around the relative treatment effect of ibrutinib versus PC. This issue is discussed in further detail in the subsequent section.

Clinical inputs for PC – indirect treatment comparison

In the FAD for TA491,[3] the Appraisal Committee highlighted concerns regarding uncertainty around the estimated relative treatment effect on PFS for ibrutinib versus standard treatments. The ToE document for the CDF review states *"The company should fully explore the most appropriate comparison based on data collected during the period of managed access, with particular focus on whether data from iNNOVATE can be used to establish the relative effectiveness of ibrutinib compared to standard of care."*[6] The CDF model does not include any alternative or updated estimates of the relative treatment effect of ibrutinib on PFS; the original HR from the matched ITC is retained and is assumed to be transportable to the SACT population represented in the CDF model. The condition set out in the ToE has therefore not been met.

More mature data are available from the later data-cut of Study 1118E[14] and from RMR,[11] which could have been used to inform updated ITCs for PFS. Whilst IPD from these sources are not available, NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 outlines various population-adjustment methods which do not require IPD from multiple treatment groups.[37] In their response to a request for clarification from the ERG (question A1),[13] the company highlighted two disadvantages associated with using these population-adjustment methods: (i) undertaking new ITCs using the longer-term data from Study 1118E or RMR would require additional assumptions because they would involve unanchored comparisons, and (ii) with respect to the RMR dataset, variations in covariates would likely impact on the effective sample size (ESS).

Regarding the first limitation, the ERG notes that the company's original ITC,[1] which used a multivariable Cox model based on matched data between the earlier data-cut of Study 1118E[2] and the ECR,[4] also took the form of an unanchored comparison. As such, the company's original ITC and the alternative population-adjustment methods described in TSD 18[37] rely on the same assumption that all effect modifiers and prognostic factors are accounted for. The ERG notes that the covariate information from RMR[11] is limited; hence, undertaking new ITCs using this source is likely to be at high risk of confounding. The ERG notes however that baseline covariate information from Study 1118E is available and could, in principle, have been used to inform a matching-adjusted indirect comparison (MAIC), using Study 1118E as the aggregate dataset and the ECR as the IPD dataset. This would have allowed for the longer-term data from Study 1118E to be included in the analysis (for example, by estimating time-varying HRs for PFS between the later data-cut of Study 1118E and re-weighted PFS data for the ECR group). It is unclear whether a similar analysis could have been undertaken using iNNOVATE Arm C; this dataset is not discussed in the company's clarification response.[13] The ERG agrees with the company that SACT[10] could not be used in an updated ITC because it does not provide data on PFS.

Regarding the second limitation, the ERG acknowledges that the difference in the joint distribution of covariates between ECR and RMR might lead to insufficient overlap to apply the alternative population-adjustment methods. The company suggests that the impact of variation in covariate information will likely impact on ESS. The ERG notes that ESS will only be influenced if a re-weighting method is used; if a simulated treatment comparison (STC) was undertaken, ESS would be unaffected.

Overall, the ERG accepts that the data available to undertake further ITCs are subject to limitations and that these may preclude the company from generating reliable estimates of relative treatment effects on PFS for ibrutinib versus standard treatments. However, the ERG believes that the company should still have attempted these additional analyses and that they could have explored their impact in scenario analyses within the economic model. The ERG also notes that their clinical advisor commented that the HR obtained from the company's original ITC was lower (more favourable) than expected and that it may represent an overestimate.

4.2.5 Critique of other amendments to model inputs

The ERG believes that the other updated model parameters included in the CDF model are generally appropriate. The ERG had some concerns regarding the inclusion of markedly higher unit costs for the management of some AEs (lung toxicity, diarrhoea and constipation) in the CDF model compared with the TA491 model. However, as highlighted in the company's clarification response[13] (question B11), these do not have a material impact on the ICER.

4.3 ERG's exploratory analyses

This section presents the methods and results of the exploratory analyses undertaken by the ERG. All analyses use the confidential PAS price for ibrutinib ([redacted] per 140mg capsule). All ICERs presented in this section are based on the deterministic version of the model.

4.3.1 ERG exploratory analysis - methods

The ERG undertook four exploratory analyses. These include the ERG-preferred analysis and three additional sensitivity analyses (ASAs):

- ERG-preferred analysis: PPM for ibrutinib based on SACT,[10] PFS for ibrutinib modelled using HR for TTD versus PFS from RMR[11] applied to TTD model from SACT,[10] PPS probabilities re-calibrated to fit OS data from SACT
- ASA1: ERG preferred analysis plus PFS = TTD
- ASA2: ERG preferred analysis plus treatment effect HR = 0.50
- ASA3: ERG preferred analysis plus treatment effect HR = 0.75

These analyses are described further in detail below.

ERG-preferred analysis

The ERG's preferred analysis involves a combination of three model amendments:

(i) PPM for ibrutinib was set equal to the on-treatment mortality rate from SACT.[10] As noted in Section 4.2.4, this is expected to be an underestimate of the true PPM rate.

(ii) PFS for the ibrutinib group was estimated by calculating the HR between TTD and PFS in the RMR dataset[11] based on a comparison of the exponential survival models fitted to these data (HR=[redacted]) and then applying the inverse of this HR to the TTD model fitted to data from SACT.[10] This results in a smaller gap between TTD and PFS compared with the company's CDF base case model.

(iii) PPS probabilities applied in the 3L, 4L and BSC states were re-calibrated by minimising the SSE between the observed Kaplan-Meier function for OS from SACT[10] and the OS model projection for the ibrutinib group in the CDF model. Together with the other two amendments, this re-calibration process reduces the PPS adjustment factor from 8.97 to 3.31 (i.e. patients survive longer following progression).

These amendments were not implemented separately as the company has already assessed the use of PPM from SACT[10] in their scenario analyses (see Table 15) and amendments (i) and (ii) both require the PPS probabilities to be re-calibrated to obtain meaningful results. The resulting predictions of TTD, PFS and OS from the ERG's preferred analysis are presented graphically in Appendix 1.

ASA1: ERG preferred analysis with PFS = TTD

This analysis is the same as the ERG's preferred analysis, except that PFS is assumed to be equal to TTD. This analysis also requires re-calibration of the PPS risk; the resulting PPS adjustment factor is reduced from 3.31 to 2.61.

ASA2: ERG preferred analysis with treatment effect HR = 0.50

This analysis is the same as the ERG's preferred analysis, except that the HR for PFS is assumed to be 0.50. This analysis does not require re-calibration of PPS probabilities as the HR only impacts on outcomes for the PC group.

ASA3: ERG preferred analysis with treatment effect HR = 0.75

This analysis is the same as the ERG's preferred analysis, except that the HR for PFS is assumed to be 0.75. Again, this analysis does not require re-calibration of PPS probabilities.

Technical details for implementing the ERG's exploratory analyses are presented in Appendix 2.

4.3.2 ERG exploratory analysis – results

Table 17 presents the results of the ERG's exploratory analyses. As shown in the table, the three amendments which comprise the ERG's preferred analysis lead to an estimated ICER of [redacted] per QALY gained; this is higher than the company's base case ICER of [redacted] per QALY gained. This increase in the ICER is largely a consequence of the alternative approach used by the ERG to derive PFS for the SACT population, which reduces the estimated incremental QALY gain for ibrutinib versus PC from [redacted] to [redacted] QALYs. This reduction in QALYs occurs because reducing PFS in the ibrutinib group reduces the PPS risk, which then extends OS in the PC comparator group. ASA1 assumes that PFS is equal to TTD; the ICER for this analysis is estimated to be [redacted] per QALY gained. The ICER is higher for this scenario because PFS for ibrutinib and PPS risks are both lower than in the ERG-preferred analysis. The additional sensitivity analyses in which the relative treatment effect for ibrutinib is reduced to 0.50 and 0.75 (ASA2 and ASA3) lead to higher ICERs of and [redacted] per QALY gained, respectively. Whilst the values used in these scenarios are arbitrary, they demonstrate the impact of making less favourable assumptions about magnitude of the relative treatment effect on PFS on the ICER.

Table 17: ERG exploratory analysis results

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's CDF base case model (deterministic)							
Ibrutinib	5.55	[redacted]	[redacted]	4.16	[redacted]	[redacted]	[redacted]
PC	1.39	[redacted]	[redacted]	-	-	-	-
ERG-preferred analysis							
Ibrutinib	4.86	[redacted]	[redacted]	2.88	[redacted]	[redacted]	[redacted]
PC	1.98	[redacted]	[redacted]	-	-	-	-
ASA1: ERG preferred analysis plus PFS = TTD							
Ibrutinib	4.29	[redacted]	[redacted]	2.05	[redacted]	[redacted]	[redacted]
PC	2.24	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis plus treatment effect HR = 0.50							
Ibrutinib	4.86	[redacted]	[redacted]	2.34	[redacted]	[redacted]	[redacted]
PC	2.53	[redacted]	[redacted]	-	-	-	-
ASA3: ERG preferred analysis plus treatment effect HR = 0.75							
Ibrutinib	4.86	[redacted]	[redacted]	1.78	[redacted]	[redacted]	[redacted]
PC	3.08	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ASA - additional sensitivity analysis; CDF - Cancer Drugs Fund; ERG - Evidence Review Group; HR - hazard ratio; PC – physician's choice; PFS - progression-free survival; TTD - time to treatment discontinuation
** Undiscounted*

5. END OF LIFE

The CDF-CS does not make a case that ibrutinib meets NICE's criteria for life extending therapies given at the end of life.

6. DISCUSSION

The company submitted new clinical evidence from four key data sources: Study 1118E; iNNOVATE Arm C; SACT, and RMR. Naïve comparisons of Kaplan-Meier estimates of PFS across each data source indicate lower PFS probabilities in the RMR cohort than in Study 1118E and iNNOVATE Arm C. SACT does not collect data on disease progression and therefore PFS data are not available from this source. OS data were available from all four data sources. Median OS was not reached in any data source. At 24 months, the proportion of patients still alive was 95% and [redacted] in Study 1118E and iNNOVATE arm C, respectively, versus [redacted] and 73% in the RMR and SACT datasets, respectively. Despite the availability of additional clinical data collected during the period in which ibrutinib has been available through the CDF, the company's ITC has not been updated in the CDF-CS and the company's economic model retains the HR for PFS used in the original model developed to inform TA491.

The company's CDF model uses data from SACT, where available, with the intention of better reflecting clinical practice in England. The company's model suggests that the probabilistic ICER for ibrutinib versus PC is [redacted] per QALY gained; the deterministic ICER is slightly lower at [redacted] per QALY gained. The ERG believes that the company's approach for deriving PFS for the ibrutinib group using data from RMR and SACT is inappropriate. In addition, the ERG considers that the model predictions of health state occupancy in the CDF model are not clinically plausible. The ERG's preferred analysis involves re-estimating PFS for the ibrutinib group; this also impacts on the other model predictions. The ERG's preferred analysis leads to an ICER for [redacted] per QALY gained. This analysis still relies on the company's ITC, which should be considered highly uncertain. The ERG's additional sensitivity analyses indicate that if the HR is 0.50, the ICER increases to [redacted] per QALY gained; if the HR is 0.75, the ICER increases to [redacted] per QALY gained. Further expert opinion would be valuable to obtain expectations of PFS and OS for the PC group which could be used to assess the reliability of the HR obtained from the ITC.

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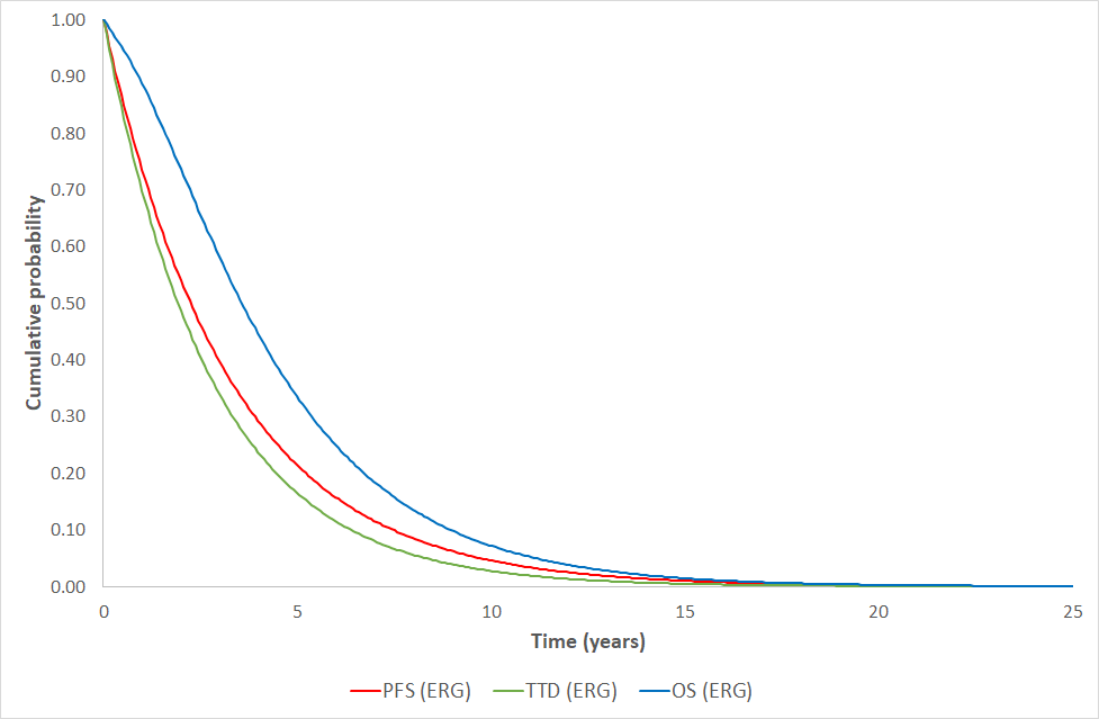
8. APPENDICES

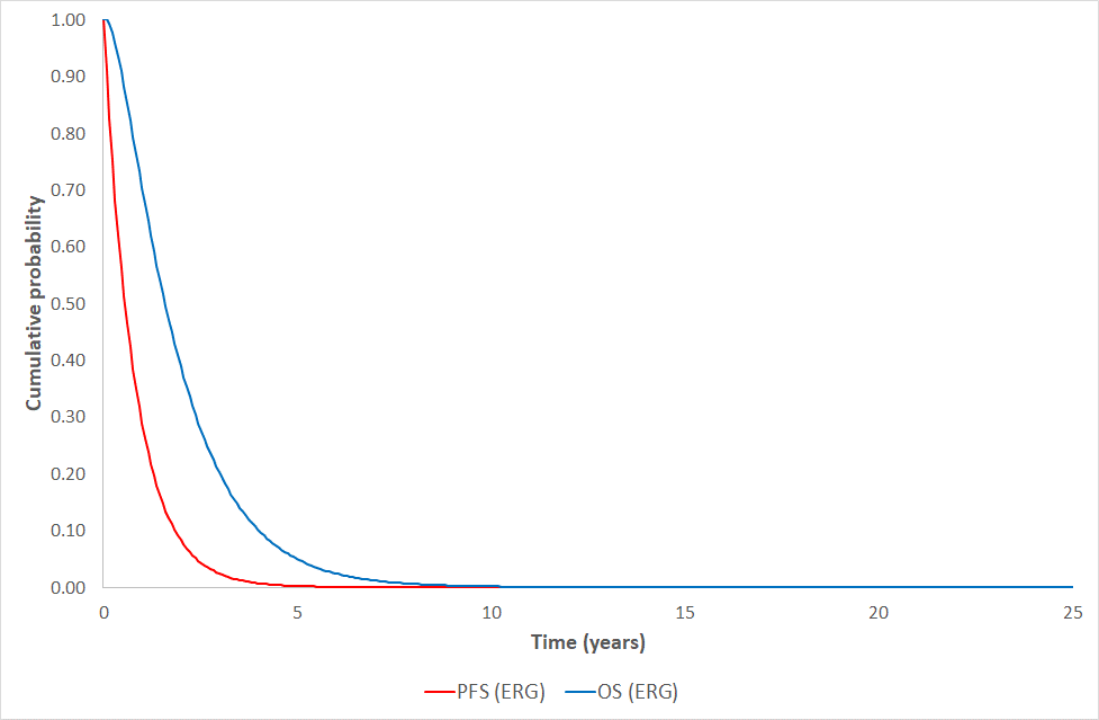
Appendix 1: Model-predicted TTD, PFS and OS from ERG's preferred analysis

Figure 14: Model-predicted TTD, PFS and OS from ERG-preferred analysis, ibrutinib group



ERG - Evidence Review Group; TTD - time to treatment discontinuation; PFS - progression-free survival; OS - overall survival

Figure 15: Model-predicted TTD, PFS and OS from ERG-preferred analysis, PC group



ERG - Evidence Review Group; TTD - time to treatment discontinuation; PFS - progression-free survival; OS - overall survival
Note: TTD is assumed to be equal to PFS

Appendix 2: Technical appendix detailing implementation of ERG exploratory analyses

The ERG has amended the company's model to alter the way that the calibration works. The following steps describe the implementation of the ERG's exploratory analyses using this amended version of the model. It is possible to generate the same results using the company's CDF model, by changing the value of the PPS mortality adjustment directly (without reference to the ERG's additional worksheet).

ERG preferred analysis

Go to worksheet "Clinical Inputs"

Set PPM equal to SACT on-treatment mortality using drop-down menu in cell I48

Set PFS equal to TD using drop-down menu in cell I24

Go to worksheet "SACT"

In cell N82, replace the formula with "H82^(1/[redacted])"

Fill the formulae down

Go to new worksheet "ERG OS fit"

Go to cell N2 (named reference "c.input_SACT.pps.hazard.adj")

Set the value of this cell equal to 3.31

ASA1

Start from ERG preferred analysis described above

Go to worksheet "SACT"

In cell N82, replace the formula with "=H82"

Go to new worksheet "ERG OS fit"

Go to cell N2 (named reference "c.input_SACT.pps.hazard.adj")

Set the value of this cell equal to 2.61

ASA2

Start from ERG preferred analysis

Go to worksheet "Options"

Set cell F40 equal to 0.50

ASA3

Start from ERG preferred analysis

Go to worksheet "Options"

Set cell F40 equal to 0.75

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3741]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 18 August 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Rory Morrison Registry cohort definition

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG referred to the Rory Morrison Registry (RMR) cohort as receiving ibrutinib as a second-line treatment on: Page 17: "Of these, 112 patients had received or were receiving ibrutinib as a second-line treatment (see CDF-CS, page 15);[…]"	Janssen suggests the following wording instead: "Of these, 112 patients had received or were receiving ibrutinib ~~as a second-line treatment~~ in the relapsed/refractory setting (see CDF-CS, page 15);[…]"	In CDF-CS, Table 4 "Secondary sources of clinical evidence" (page 15) specified twice that patients from the RMR cohort have received ibrutinib in the relapsed/refractory setting: • Population: "WM patients with at least one prior line of therapy • Inclusion: "Ibrutinib monotherapy as ≥ 2nd line of therapy".	We agree. As requested, the text has been amended to read "second- and subsequent-line" throughout the report.

Issue 2 Rory Morrison Registry cohort age

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG stated that median age was not reported for the RMR cohort on: Page 9: "Median age is not reported for WM patients with prior therapy in the RMR cohort" Page 18: "Median age was not reported for patients with prior therapy in the RMR cohort."	Janssen suggests the following wording instead: "Median age was ~~not~~ reported to be [redacted] years (range: [redacted]) for WM patients with prior therapy in the RMR cohort (n=112) (see Appendix B.2, page 35 and B.3, page 41)."	Median age for the RMR cohort was presented in the CDF-Appendices (B.2 Table 12 page 35, B.3 page 41). Median age is [redacted] years (range: [redacted]) for the RMR n=112 cohort.	We agree. The text has been amended as requested.

Issue 3 INNOVATE trial arm C cohort definition

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG stated that Arm C of the iNNOVATE trial includes untreated patients: Page 8 :"[…] updated efficacy data from Study 1118E and Arm C of the iNNOVATE trial (this relates to the ibrutinib monotherapy arm for patients with untreated and previously treated WM that is refractory to rituximab)."	Janssen suggests the following wording instead: "[…] updated efficacy data from Study 1118E and Arm C of the iNNOVATE trial (this relates to the ibrutinib monotherapy arm for patients with ~~untreated and~~ previously treated WM that is refractory to rituximab)."	INNOVATE trial arm C includes only previously treated patients. This is captured in CDF-CS Table 4 "Secondary sources of clinical evidence", page 15: "Population: Arm C: WM patients who relapsed within 12 months of last rituximab-containing treatment or who failed to respond to rituximab-containing therapy and not eligible for randomisation."	We agree. The text has been amended as requested.

Issue 4 Clinical validation of modelled PFS & OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG stated that the output of the clinical validation process for modelled PFS and OS was not provided (in the CDF-CS). The following statement were made on page 31 and page 33 on modelled PFS and OS respectively: Page 31: "The company's clarification response (question B4) states that the four clinical experts who provided judgements about the plausibility of the SACT TTD	Janssen suggests the second statements provided on page 31 and page 33 of the ERG report (which are exactly the same) be replaced with the following wording: "~~No details are provided regarding~~ While the output of the validation exercise was presented, ~~or~~ no details were provided on the means by which any potential concerns raised	Modelled PFS was validated by clinicians as explained in CDF-CS pages 29-30: "The exponential and Weibull curves remained the most conservative extrapolations, with the exponential selected for the base-case to align with the unadjusted RMR PFS approach. […] The resulting curve was	We disagree. For both PFS and OS, it appears that the clinicians were presented with the model predictions for PFS and OS (based on the exponential TTD function), and no alternative projections using other models. The CS states that the models were "validated by clinician insights" but does not provide any information about the outputs of

model were also asked to validate the derived PFS model. No details are provided regarding the output of the validation exercise or the means by which any potential concerns raised by individual experts, or disagreements between them, were addressed." Page 33: "As with the modelled PFS function for ibrutinib, the company asked the four clinical experts who provided judgements about the plausibility of the SACT TTD survival distributions to also validate the modelled OS predictions. No details are provided regarding the output of the validation exercise or the means by which any potential concerns raised by individual experts, or disagreements between them, were addressed."	by individual experts, or disagreements between them, were addressed."	validated by clinician insights." Modelled OS was validated by clinicians as explained in Appendix B.5.3 page 50: "The final selection chosen was the exponential, which was validated by clinicians and was consistent with the approach being used to extrapolate SACT TD." Janssen acknowledges there is a typological error in this sentence on page 50 and that "selection" should be replaced with "extrapolation". Of note, clarification question B4 relates to the approach and did not request specific detail on the output of the clinical validation process.	this exercise e.g. whether the experts suggested expectations of PFS/OS at certain timepoints, how discrepancies between the modelled estimates and the experts' expectations were addressed, or how any disagreements between their views were resolved. This information is also not presented in the clarification response. The text has not been amended.

Issue 5 Incorrect PSA results reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG presented the following results for the company probabilistic sensitivity analysis (PSA): On page 10: "The probabilistic version of the company's CDF	Janssen suggests all results presented in the ERG report on the company PSA are updated in line with those presented in CDF-CS Table 12 page 36 (here pasted in transposed format to accommodate the format of the factual accuracy form): **Table 1. Probabilistic base-case results (PAS price) – B.1.5 (page 19)**	The information presented in the ERG report on the company PSA results reflects neither those presented in CDF-CS Table 12 page 36 nor those generated by the company	This is not a factual inaccuracy. We re-ran the PSA using the company's submitted model. This was necessary to check the integrity of the model results, but also because

base case model suggests that ibrutinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained." On page 37: "The probabilistic version of the model suggests that ibrutinib is expected to generate an additional QALYs at an additional cost of [redacted] per patient; the corresponding ICER is [redacted] per QALY gained" On page 54: "The company's model suggests that the probabilistic ICER for ibrutinib versus PC is [redacted] per QALY gained" The detail of the results from the probabilistic model is also provided in Table 14 page 38.	<table><tr><th>Technologies</th><th>Ibrutinib</th><th>Physician's choice</th></tr><tr><td>Total costs (£)</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Total LYG</td><td>3.89</td><td>1.45</td></tr><tr><td>Total QALYs</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Incremental. costs (£)</td><td>[redacted]</td><td>-</td></tr><tr><td>Incremental LYG</td><td>2.44</td><td>-</td></tr><tr><td>Incremental QALYs</td><td>[redacted]</td><td>-</td></tr><tr><td>Incremental ICER (£/QALY)</td><td>[redacted]</td><td>-</td></tr><tr><td colspan="3">ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life years</td></tr></table>	CDF cost-effectiveness model submitted alongside the CS-CDF and labelled "CDF Review_Janssen_Submission_ID3778 _ibrutinib_WM_Model_7Jul 2021_ACIC".	we consider it more appropriate to report undiscounted LYGs (the CDF-CS reports only discounted LYGs). The ERG's results are slightly different to those in the CDF-CS because the company's model does not use the same set of random numbers across PSA runs. We have clarified in the text that the results are based on a re-run of the PSA by the ERG.

Issue 6 Company rationale for anchoring base-case to SACT cohort

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG stated on page 41: "Whilst not explicitly stated in the CDF-CS or its appendices, the company's	Janssen suggests the following wording instead: As explained both in the CDF-CS (page	The decision Janssen made to anchor the new company base-case to the SACT cohort was	We agree. The text has been amended in line with the company's suggestion.

clarification response (question B3) indicates that the company's intention was to use the model submitted for the CDF review to reflect the SACT population in order to better represent clinical practice in England."	33) and in ~~Whilst not explicitly stated in the CDF-CS or its appendices,~~ the company's clarification response (question B~~3~~1), ~~indicates that~~ it was the company's intention ~~was~~ to use the model submitted for the CDF review to reflect the SACT population in order to better represent clinical practice in England"	guided by the Data Collection Arrangement (DCA) that underpins the Managed Access Agreement (MAA) in place for the CDF funding of ibrutinib in relapsed/refractory WM; the DCA states on page 5 that "The primary source of data collection during the MAA period will be the SACT dataset".[1] This is further supported by the Terms of Engagement document (May 2021) page 5: "SACT data collected within the Cancer Drugs Fund by Public Health England will provide data on patient baseline characteristics, treatment duration and overall survival. It will support the generalisability of the Study 1118E data." Janssen's intention to use the model submitted for the CDF review to reflect the SACT population in order to better represent clinical practice in England was explicitly stated in CDF-CS page 33: "While the new company base-case was primarily based on SACT data to ensure that outcomes are most	

[1] https://www.nice.org.uk/guidance/ta491/resources/managed-access-agreement-november-2017-pdf-4664622781.

		representative of English clinical practice for the treatment of WM, data from the RMR and Study 1118E were also leveraged where necessary." In addition, and throughout the CDF-CS, it has also been explained, though in separate statements, that: i) The CDF model base-case was built around SACT: On page 7: "Janssen has built its new company base-case around the 3-year data from SACT, which the DCA defined as the primary data source for this CDF review". ii) SACT was deemed the data source most representative of English national clinical practice: On page 13: "The SACT database has collected data on 823 patients with WM from Trusts in England and is therefore deemed the source most generalisable to NHS clinical practice." These statements from the CDF-CS are in line with	

		Janssen's clarification response (question B1). Please note clarification question B3 relates to the drug acquisition costs used in the model.	

Issue 7 ERG wording on CDF model PC arm OS projection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 6, the ERG summarises the company CDF model OS projection for the PC arm as follows: "The model predicts that virtually all PC-treated patients will have died after around 6 years after starting initial treatment for R/R WM. The ERG's clinical advisor believed this was unrealistic as some patients survive beyond 6 years."	Janssen suggests the following wording instead: "The model predicts that virtually all PC-treated patients (99.6%) will have died after around 6 years after starting initial treatment for R/R WM. The ERG's clinical advisor believed this was unrealistic as some patients (please provide percentage) survive beyond 6 years."	Janssen considers that the fact the model projects that "virtually all" PC-patients will have died at around 6 years does not contradict the ERG's clinical advisor opinion that "some patients" survive beyond 6 years. This ERG statement would gain clarity if the quantification of patients that have died vs are expected to die was expressed using percentages for the model output and the ERG's clinical advisor opinion respectively.	This is not a factual inaccuracy. Given that the model predicts a probability of PC-treated patients remaining alive at 6 years of 0.004, we consider it reasonable to state that virtually all patients have died. For clarity, we have amended the text to state the percentage of patients remaining alive at 6 years. As discussed in the ERG report, our clinical advisor did not consider the OS prediction to be clinically realistic. We will elicit estimates of the clinician's expectations of PFS and OS for PC as part of our technical engagement response.

Issue 8 Company presentation of SACT data accuracy/completeness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that Janssen provides limited information on the completeness and accuracy of the SACT data and refers to Appendix B.3. Page 17: "The CDF-CS provides limited details on the completeness and accuracy of the SACT dataset, especially with respect to clinical outcomes (CDF-CS, Appendix B.3)."	Janssen suggests the following wording instead: The CDF-CS provides limited details on the completeness and accuracy of the SACT dataset, especially with respect to clinical outcomes ~~(CDF-CS, Appendix B.3)~~. However, this information was presented in full in the SACT final report (page 15) which was shared with both Janssen and the ERG.	Janssen and the ERG both received the SACT final report ahead of the company CDF Review submission. Janssen summarised in the company's clarification response (question B2) the information presented in the SACT final report on data completeness and accuracy. Note Appendix B.3 presents a cross-source comparison of patient baseline characteristics and therefore data that is not relevant to this matter.	The SACT report was not provided in the reference pack to the CDF-CS. The key information provided in SACT is available from the CDF-CS, the clarification response and the company's model, hence this is not a problem. But it does mean that the ERG cannot comment on data completeness or accuracy beyond the information provided in the CS and accompanying documents, and the text in the ERG report remains accurate. No amendment is required.

Issue 9 FAD key areas of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG stated that ibrutinib's relative benefits in terms of PFS and OS are "key areas of clinical uncertainty" discussed in the FAD: Page 20: "The key areas of clinical uncertainty discussed in the FAD for TA4913 relate to the relative effectiveness	Janssen suggests the following wording instead: "The key areas of clinical uncertainty discussed in the FAD for TA49 relate to the relative effectiveness of ibrutinib versus current treatments in terms of PFS,	While Janssen agrees that relative benefit of ibrutinib in terms of PFS, together with the modelling of PPM, were identified by the FAD as "key areas of uncertainty", Janssen also understands that the uncertainty	This is not a factual inaccuracy. The original appraisal recognised uncertainty around the effect of ibrutinib in terms of both PFS and OS. Section 4.7 states *"However, it also concluded that the longer-term effects on progression and*

of ibrutinib versus current treatments in terms of PFS and OS." The ERG consequently structured Section 3 "Clinical effectiveness" of its report around PFS (Section 3.2) and OS (Section 3.3), and covered the TD and pre-progression mortality (PPM) outcomes together in the last sub-section (3.3).	~~and OS~~ as well as the modelling of ibrutinib PPM; uncertainty around the ibrutinib OS benefit was also raised but in the context of ibrutinib PPM."	around ibrutinib OS benefit was mentioned in the FAD, yet in the context of the modelling of ibrutinib PPM. The key areas of uncertainties for CDF Review of TA491 are summarised in the FAD page 18-19 and relate to both PFS (FAD section 4.8) and PPM (FAD section 4.11). While the FAD statement around the "size of the long-term benefit of ibrutinib" is broad, and could, without context, be interpreted as including both PFS and OS, in the FAD it is presented in relation with the indirect treatment comparison (Section 4.8), which relates to PFS only. WM is an indolent disease, with the clinical literature reporting a median OS of 4-12 years, and unfortunately no data on comparator treatments can be collected within the CDF. As such, uncertainty around relative OS benefit of ibrutinib was not "resolvable" within the timeframe of the CDF data collection period.	*survival are uncertain because no data are available."* The ERG report has not been amended.

Issue 10 ERG arbitrary hazard ratio values for updated PFS indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has criticised that the PFS indirect treatment comparison (ITC) used in the FAD base-case has not been updated in the CDF company base-case using data from study 1118E longer follow-up. To test the impact on the ICER of using an updated ITC, the ERG has conducted two scenario analyses in which the ibrutinib PFS relative treatment effect (hazard ratio [HR]) used in the company base-case (0.25) has been varied to 0.50 and 0.75 (in ASA2 and ASA3 respectively). The ERG specified that the HR values used in the two scenario analyses are arbitrary: On page 52: "Whilst the values used in these scenarios are arbitrary, they demonstrate the impact of making less favourable assumptions about magnitude of the relative treatment effect on PFS on the ICER."	Janssen suggests adding the following statement after the sentence on page 52 to provide additional context on the range of HRs tested by the ERG in ASA2 and ASA3: "Of note, the HR values tested in these two scenarios fall outside the confidence intervals (95% CI: [redacted]-[redacted]) of the PFS HR ([redacted]) for ibrutinib and rituximab vs rituximab in the iNNOVATE trial."	Janssen questions the appropriateness of using the range of HRs in the ERG scenarios ASA2 and ASA3 for the following reasons: 1) The ERG did not provide a clear clinical rationale for the two arbitrary HR values tested in ASA2 and ASA3, specifically why longer trial follow-up data would translate into less favourable HRs. Furthermore, if worse HRs are tested, it is also valid to test better HRs. 2) The maximum HR value, tested in ASA3 (0.75), represents a three-fold increase compared to the value used in the FAD base-case (0.25), which was endorsed by the Committee and was based on a shorter follow-up of the same trial (study 1118E) and therefore lacks plausibility. 3) In the absence of any new or updated comparative efficacy evidence in the RR WM population following the CDF data collection period, results for the randomised arms of the iNNOVATE trial, an RCT in patients with WM, can be	This is not a factual inaccuracy. We believe that it is reasonable to present scenarios which use less favourable assumptions about the relative effect on PFS for ibrutinib versus standard treatments. This is not because more follow-up would reduce the HR, but rather that the HR is itself highly uncertain. As noted in Issue 7, our clinical advisor did not consider the company's model predictions to be clinically plausible as virtually all PC-treated patients are predicted to die within 6 years. These scenarios result in less pessimistic results for PC, and this HR is the only model parameter used specifically to predict outcomes in the PC group. We do not believe that the HR and 95% CI from iNNOVATE help to contextualise the relative treatment effect for PFS for ibrutinib and notes that the company has selected not to use these data in their model. We also note that the HR used in ASA2 does fall within the 95% CI obtained from the company's indirect

		used to contextualise the relative PFS treatment effect for ibrutinib. The HR values tested in the ERG ASA2 (0.50) and ASA3 (0.75) fall outside the confidence intervals for the PFS benefit demonstrated in iNNOVATE for ibrutinib and rituximab vs rituximab, which shows an HR of [redacted] (95% CI: [redacted])[2], i.e. a benefit in line with the FAD HR of 0.25. At technical engagement, Janssen will explore update to the ITC with the latest trial data from Study 1118E, as discussed by the ERG, and despite limitations in doing so, which were outlined in Section A.7 of the CDF-CS. This will provide a further sensitivity analysis on the relative PFS benefit of ibrutinib vs PC. Janssen do not however consider a three-fold increase in the HR to be clinically plausible nor particularly informative for decision-making.	comparison. The ERG report has not been amended.

There were no errors in the marking of confidential information contained within the ERG report.

Additional note from the ERG: A small number of minor editorial amendments have also been applied to the final ERG report

[2] Source: PCYC Clinical study report for iNNOVATE (20 April 2020), Janssen confidential data

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Technical engagement response form

Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Thursday 16 September 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen-Cilag Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: evidence used to inform the company's CDF model remains highly uncertain. The company's CDF model uses evidence from multiple data sources as no single source provides information on all clinical inputs. Of particular importance, SACT does not collect PFS data, yet the company's economic model assumes that the treatment effect for ibrutinib versus PC is on PFS. For this reason, the company instead derived	**YES**	**Issue 1a – modelling ibrutinib PFS** Janssen anchored its company CDF base-case analysis to the SACT cohort (n=823), as this cohort is deemed most representative of the English RR WM population treated in the NHS setting. This is in line with both the Data Collection Arrangement that underpins the Managed Access Agreement in place for ibrutinib treatment via the CDF, as well as the Terms of Engagement which summarise NICE's requirements for CDF review of TA491. One of the key challenges of this CDF review is the modelling of ibrutinib progression-free survival (PFS) for the SACT cohort in the absence of SACT PFS data. The CDF data collection process however gave Janssen an opportunity to collect additional ibrutinib data in patients from the Rory Morrison Registry (RMR) (n=112), the only national WM-specific registry, and which represent a subset of the SACT population. In its CDF company base-case, Janssen used data from the RMR to derive the modelled PFS for the SACT cohort using an approach which can be summarised as follows: a hazard ratio was derived between RMR treatment duration (TD) and SACT TD, which was then applied to RMR PFS to generate SACT "derived" PFS. In its preferred analysis, the ERG combined the SACT and RMR data in a different way to estimate ibrutinib PFS, whereby a hazard ratio was estimated between the RMR PFS and RMR TD which was then applied to SACT TD to generate SACT "derived" PFS. Jansen appreciates that the approach followed by the ERG does improve the face-validity of the company CDF model base-

PFS for the SACT population using external data from RMR and assumptions (as described in the bullet points in Section 1.5). The ERG does not consider the company's approach for deriving PFS to be appropriate and notes that it leads to implausible model predictions (see Issue 2). In addition, the Terms of Engagement (ToE) for the CDF review state that *"the company should fully explore the most appropriate comparison based on data collected during the period of managed access, with particular focus on whether data from iNNOVATE can be used to establish the relative effectiveness of ibrutinib compared to standard of care."* This has not been done and the CDF model uses the HR obtained		case results (see Issue 2 below) and therefore accepts this methodology for use in its revised company base-case. Therefore, the revised company base-case ICER is [redacted]/QALY using ibrutinib patient access scheme (PAS) price. Recognising the limitations in deriving ibrutinib PFS where no SACT PFS data is available from the SACT 3-year (final) report, and acknowledging that TD is not a suitable proxy for PFS, Janssen has independently commissioned analyses from Public Health England (PHE) on ibrutinib time-to-next-treatment (TTNT) to help further address this uncertainty. Given clinical insights have suggested that RR WM patients treated with ibrutinib switch treatment shortly after they progress, Janssen considers that ibrutinib TTNT data can provide an upper boundary for where the "true" ibrutinib SACT PFS may lie. Janssen has also noted in the submission made by the professional groups for this CDF review that it was suggested that TTNT may also be a relevant clinical endpoint for consideration in WM patients. The TTNT analyses were conducted on the same SACT cohort (n=823) used to derive the analyses in the SACT final report for ibrutinib in WM and which results were presented in the company CDF review submission (July 2021). Median TTNT was estimated at [redacted] months (95% CI: [redacted]), compared with 24.9 months for median TD in the final SACT report. XXXXXXX1 below presents side by side the SACT TTNT KM plots with the KM for TD and overall survival (OS) presented in the SACT final report.

from the company's original ITC in TA491. The ERG believes that it would have been possible to undertake a population-adjusted ITC for PFS using the longer-term data from Study 1118E and the ECR. It is unclear whether a similar comparison could have been implemented using data from iNNOVATE Arm C. The ERG accepts that the data available to undertake further ITCs are subject to important limitations and that these may preclude the company from generating reliable estimates of relative treatment effects. However, the ERG considers that the company should still have attempted to perform these analyses and that these could have been explored in scenario		[redacted] [redacted] [redacted] Additional information on the methods for the TTNT analyses are presented in Appendix 1. TTNT data was used as a proxy for ibrutinib PFS in a scenario analysis as follows: patient-level data for TTNT were fitted with six standard parametric models. The exponential distribution was selected as it best matched the TTNT KM curve visually and it was also used to model SACT TD in the company CDF Review submission. Extrapolated TTNT was then assumed to represent PFS for ibrutinib. Further detail on how the TTNT data was incorporated in the scenario analysis is presented in Appendix 1. The results for this analysis using PAS price are shown in Table 1 below:

analyses using the economic model.
The ERG notes that although additional data have been collected during the period in which ibrutinib has been available through the CDF, these have not been used to reduce uncertainty around the relative clinical benefit of ibrutinib versus PC.

Table 1. Cost-effectiveness results: revised company base-case vs TTNT scenario

Analysis	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Revised company base-case [ERG settings]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base-case with ibrutinib PFS = TTNT	[redacted]	[redacted]	[redacted]	[redacted]

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life year gained; PC, physician's choice; PFS, progression-free survival; QALY, quality-adjusted life year; TTNT, time to next treatment.

Note: * Undiscounted.

This scenario yields an ICER of [redacted]/QALY, which is significantly lower than the revised company base-case ICER of [redacted]/QALY.

In summary, in the absence of SACT PFS data, and whilst neither TD nor TTNT can be deemed "perfect" proxies for progression, TTNT data is useful for decision making as it represents the upper bound of progression thus narrowing the range of uncertainty for decision-making. As such, PFS is likely to lie somewhere in the middle.

Issue 1b – Indirect treatment comparison

In the original NICE company submission (2016), the relative PFS benefit of ibrutinib vs Physicians' choice (PC) was modelled using an indirect treatment comparison (ITC) based on patient level data (PLD) from both study 1118E (n=63) 24-month data-cut and from a large pan-European observational study (n=454) in WM (referred to as the European Chart review [ECR]) for ibrutinib and PC respectively. The ITC, which yielding a HR of [redacted] for PFS, was accepted by the Committee in the FAD, acknowledging that "*there remains considerable uncertainty about the size of the long-term benefit because of limitations in the data available*". Hence ibrutinib's relative PFS treatment effect was identified as a key area of uncertainty for the CDF review of TA 491.

		As explained in company CDF review submission Section 7, given "*no comparative efficacy data can be collected through SACT, there is limited new evidence to address uncertainty in the ITC, and the analysis cannot be updated or improved with the use of other data sources either. Indeed, the uncertainty in the ITC cannot be reduced with longer follow-up data from Study 1118E because, given this is an IIS, no further PLD are available. Using aggregated evidence from the published 59m data-cut would therefore only incorporate greater uncertainty into the analysis*." Following the review of the ERG report, Janssen stands by this position and believes the ITC used in the FAD, which is also used in the ERG preferred analysis, is the most appropriate estimate to capture ibrutinib relative PFS benefit in its revised company base-case. <u>Updated ITC (MAIC) using Study 1118E long-term data</u> Janssen has however explored updating the FAD ITC with Study 1118E long-term data in line with the ERG suggestion for key Issue 1b, and so as to contextualise the FAD ITC. The ITC analysis was updated based on aggregated 59-month follow-up (FU) data for Study 1118E published by Treon *et al.* 2020.[1] Since the only data available was a published Kaplan-Meier (KM) curve for PFS, the adjustment for important prognostic factors was done through matching-adjusted indirect comparison (MAIC) (i.e. ECR cohort was re-weighted to match baseline characteristics of the Study 1118E cohort). In the updated ITC analysis, published data on patient characteristics and outcomes from Study1118E on ibrutinib monotherapy and PLD for PC from ECR (n=397) were used for analyses. Prognostic factors considered for matching were those for which data were available across the two data source and listed by clinical experts as important prognostic factors. They are the same as for the FAD ITC and are presented in Table 2 below. MAIC adjustment resulted in an ESS of 84 patients in ECR. The updated HR based on 59-month FU is [redacted] and is very closely aligned to that used in the FAD base-case, even though different statistical methodologies were used for the ITC.

[1] Treon SP, Meid K, Gustine J, Yang G, Xu L, Liu X, et al. Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia. J Clin Oncol. 2020;39(6):565-75

Table 2. Indirect comparison - summary of updates to FAD ITC

	FAD ITC	MAIC
HR for ibrutinib vs PC	[redacted]	[redacted]
Sample size/ESS	175	84
Study 1118E data-cut (median)	24 months	59 months
PLD available?	Yes	No
ITC methodology used?	Multivariate Cox Regression Analyses	MAIC
Prognostic factors used for adjustment	• Number of prior lines of therapy • Age • Sex • Serum β2-macroglobulin • Haemoglobin • Serum monoclonal IgM • Platelet count • WM International Prognostic Score Time from diagnosis	
Was missing data imputed?	Yes*	

Key: ESS: effective sample size; FAD: Final appraisal determination; HR: hazard ratio; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; PC: Physicians' choice; PLD: patient-level data

* The multiple imputation by chained equations (MICE) package in R was used to impute the missing data. For more details refer to the Appendix 2.

Janssen has conducted a scenario analysis in which the HR of [redacted] estimated by the MAIC is applied within the revised company base case (which adopts the ERG-preferred methodology for deriving PFS). These results are shown in Table 3 below:

Table 3. Cost-effectiveness results: revised company base-case vs MAIC scenario

Analysis	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Revised company base-case [ERG settings]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base-case with MAIC	[redacted]	[redacted]	[redacted]	[redacted]

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life year gained; PC, physician's choice; PFS, progression-free survival; QALY, quality-adjusted life year; TTNT, time to next treatment.

Note: * Undiscounted.

This scenario yields an ICER of [redacted]/QALY, which is approximately £2K/QALY higher than the ERG base-case ICER of [redacted]/QALY. Again, as explained below, this ICER was generated using a HR estimate based on a MAIC, which reflects that aggregated evidence only was available for the 59m follow-up. Hence Janssen believe this ICER is not informative to address the uncertainty stated by the Committee in the FAD.

Of note, further information on the methods including on the assumption of proportional hazards within the context this MAIC can be found in Appendix 2. Given the timeframe for this technical engagement response, Janssen have not explored further modelling of PFS without the reliance on the assumption of proportional hazards. Furthermore, Janssen consider that, given the similarity in ITC results between the FAD ITC and MAIC, further analysis is unlikely to reduce uncertainty or further improve face-validity of the model results.

<u>Updated ITC using iNNOVATE arm C data</u>

Janssen acknowledges the ERG's interest in using data from INNOVATE arm C sub-study (n=31) to reduce uncertainty given PLD is available for ibrutinib monotherapy. Janssen maintains, however, that further analyses with arm C data are unable to resolve uncertainty as arm C (i) represents a subset of RR WM patients refractory to rituximab and more heavily pre-treated with poorer prognosis than those in Study 1118E and SACT and (ii) only includes 31 patients so once adjustments are made for differences in patient characteristics and prognostic factors, the effective sample size would be too small to enable any meaningful analysis.

Key issue 2: The company's model predictions of health state occupancy are not plausible The company's CDF model generates estimates of health state occupancy which are very different to those from the original TA491 model. The ERG has concerns that several of the CDF model predictions are not clinically plausible: (a) Ibrutinib group: The model suggests a large gap between TTD and PFS. This gap suggests that patients experience a mean lag of 1.18 years between the time at which they discontinue treatment with ibrutinib and the time at which they progress. The ERG's clinical advisor stated that patients are	**YES**	Janssen acknowledges the importance of assessing the face-validity of model predictions. Janssen also recognises that the approach adopted by the ERG to derive and model "SACT PFS" in its preferred analysis, has been able to resolve concerns around the plausibility of the CDF model predictions. More specifically, ERG report p12 explains that the ERG preferred analysis: (a) reduced the gap between TD and PFS for the ibrutinib group, (b) increased the gap between PFS and OS for the ibrutinib group, and (c) led to higher estimates of OS for the PC group. Indeed, for this reason Janssen accepts this methodology within the revised company base-case. Additional information on the extent to which these three key concerns have been resolved is provided below. **Issue 2a – lag between ibrutinib treatment discontinuation and disease progression** The company model suggests that patients experience a mean lag of 1.18 years between the time at which they discontinue treatment with ibrutinib and the time at which they progress; in the ERG preferred analysis, the mean lag was reduced from 1.18 to 0.48 years, i.e. from about 1 year to 6 months. **Issue 2b – time between when ibrutinib patients progress and die** The company model suggests a small lag (0.42 years) between PFS and OS i.e. patients treated with ibrutinib spend almost all of their survival time without disease progression. The ERG clinical advisor deemed this lag implausible and noted that patients who progress on ibrutinib are sometimes salvageable on 3L and 4L chemotherapy. In the ERG preferred analysis, mean PFS:OS lag increased from 0.42 to 1.16 year, i.e. from around 6 months to one year. **Issue 2c – proportion of patients in PC arm expected to die at 6 years** The company model predicts that virtually all PC-treated patients (99.4%) will have died after around 6 years after starting initial treatment for RR WM. The ERG clinical advisor deems this proportion unrealistic as some patients survive beyond 6 years; the ERG preferred analysis predicts 97.6% of patients die at 6 years and therefore reduces the proportion by approximately 2 percentage points.

generally treated until progression and that those who discontinue before progression will progress after only a short period of time. (b) Ibrutinib group: The model suggests only a small gap between PFS and OS in the ibrutinib group. This suggests that patients treated with ibrutinib spend almost all of their survival time without disease progression. The ERG's clinical advisor did not consider this to be plausible and noted that patients who progress on ibrutinib are sometimes salvageable on 3L and 4L chemotherapy. (c) PC group: The model predicts that virtually all PC-treated patients (99.6%) will have died after around 6 years after starting initial		By accepting the ERG preferred analysis as a whole as its "revised" company base-case, Janssen considers that key concerns expressed by the ERG with regards to the face-validity of the CDF model predictions, reflecting the opinion of the ERG's clinical adviser, have been addressed in the "revised" company base-case. Janssen would like to make three further statements around the assessment of model face-validity, as part of the TE phase: (i) ibrutinib patient cohort in scope for this appraisal and modelled in company base-case is the SACT cohort, as it is deemed the cohort most representative of the relapsed/refractory WM population treated in the NHSE setting. This cohort includes a 61%/39% split of patients treated in 2L/3L+ setting. While Janssen acknowledges that in the future an increasing number of patients may be treated with ibrutinib at 2L, for this appraisal, the population is aligned with the SACT cohort, therefore the face-validity of the ibrutinib model predictions defined as "issue 2a&b" should be assessed against the SACT population, not the expected/future ibrutinib population in England; (ii) when putting in perspective the ibrutinib and PC outcomes generated by the TTNT analysis with those from the ERG preferred analysis, the latter are clinically plausible, based on the ERG's clinical advisor opinion, hence the ERG preferred analysis is used as revised company base-case and the TTNT analysis as a scenario; (iii) Janssen also acknowledges that the ERG face-validity assessment was primarily based, as per the ERG report, on the opinion of the ERG's clinical advisor. Janssen would be interested in seeing this opinion contextualised with perspectives from the wider WM clinical community, primarily from the WM professional groups involved in the TE phase, namely the Royal College Pathologists and the British Society for Haematology. Lastly, Janssen recognises the limitations of achieving technically robust analyses in a setting where comparative effectiveness data are scarce, as such is the case in WM, a rare and indolent disease. Nevertheless, clear steps have been taken by Janssen and the ERG to explore the optimal use of available evidence to reduce and/or resolve uncertainty where possible,

treatment for R/R WM. The ERG's clinical advisor believed this was unrealistic as some patients survive beyond 6 years.		acknowledging some areas of uncertainty are inherent to decision-problem and thus remain managed only through scenario and sensitivity analysis.

Summary of changes to the company's cost-effectiveness estimate(s)

As explained above, following the TE phase, Janssen has updated the company CDF review submission base-case analysis in line with the assumptions retained by the ERG in their preferred analysis. Therefore, the company base-case has increased from [redacted]/QALY in submission dated 07/2021 to [redacted]/QALY in the TE response. Though not captured in the table below, the change in the approach to modelling ibrutinib PFS, which relates to ERG Issue 1a, also indirectly improves the face-validity of CDF model predictions and in turn addresses ERG Issue 2.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
ERG Issue 1: The evidence used to inform the company's CDF model remains highly uncertain – Section 4.2.4 Clinical Inputs – PFS for ibrutinib.	PFS was indirectly estimated using an HR between TD in SACT and TD in RMR and applying this HR to a parametric survival model fitting to PFS data from RMR (ERG Report, p.45-46).	PFS was estimated using an HR between the exponential models for TD versus PFS in the RMR dataset and applying this HR to the TD function from SACT as a baseline (ERG Report, p.47).	The ICER in the original company submission was [redacted]/QALY and increased to [redacted]/QALY as a result of this change.
ERG Issue 1: The evidence used to inform the company's CDF model remains highly	PPM used in TA491, as reported in the FAD, was retained, as this was considered the most reliable estimate of PPM available. The rate was based on	Death while on treatment in SACT was used to represent the lower bound for PPM. This was included as it was more consistent with the overall intended	The ICER resulting from this change was [redacted]/QALY. When applied in addition to the

uncertain – Section 4.2.4 Clinical Inputs – PPM for ibrutinib.	deaths (n=3) reported in pre-progression from Study 1118E for 24-month follow-up (ERG Report, p.47).	population of the model. PPM was calculated using a parametric model fitted to the death while on-treatment KM data from SACT (ERG Report, p.47).	first change detailed above, this resulting ICER was [redacted]/QALY.
ERG Issue 1: The evidence used to inform the company's CDF model remains highly uncertain – Section 4.2.4 Clinical Inputs – OS for ibrutinib.	OS was calculated by calibrating the PPS risk estimated from the ECR in both groups such that the model predicts OS for the ibrutinib group which is consistent with the SACT OS data. This approach was necessary given the model using a state transition structure (ERG Report, p.48).	The updated approach used was to minimise the sum square error (SSE) between the observed Kaplan-Meier OS function from SACT and the model-predicted OS from the model trace. This was conducted using the built-in Excel Solver function (ERG Report, p.48).	The ICER resulting from this change was [redacted]/QALY. When applied in addition to both changes detailed above, this resulting ICER was [redacted]/QALY.
Company's preferred base case following technical engagement	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**Revised company base-case ICER resulting from combining the changes described:** [redacted] **Change from the company's original base-case ICER:** [redacted]

Key: CDF Cancer Drugs Fund; ECR: European Chart review; ERG: Evidence review group; FAD: Final Appraisal Determination; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; KM: Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS: overall survival, OTM: on-treatment mortality; PFS: progression-free survival; PPM: pre-progression mortality; PPS: post-progression survival; QALY: quality-adjusted life year; RMR: Rory Morrison Registry; SACT: Systemic anti-cancer therapy; SSE: sum square error; TD: treatment duration.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Thursday 16 September 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen-Cilag Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Appendix 1 – SACT time-to-next-treatment (TTNT) analysis

A. TTNT analysis

Janssen commissioned the collection of retrospective TTNT data from a SACT cohort which is the same as the cohort used for the analyses presented in the SACT three-year report, and which are the primary data source for this CDF review. The analysis of these data was conducted by an external consultancy with Public Health England (PHE) analysts who have access to the PHE datasets. A summary of study cohort and analyses is provided below.

Definition of study cohort

The SACT cohort was identified as follows:

- Firstly, patients diagnosed with WM were identified within SACT (irrespective of treatment received).
- This cohort was then further restricted to those patients who were analysed as part of the SACT three-year PHE report during the period 28/09/2017 and 27/09/2020. This period covers the date from which ibrutinib monotherapy was considered for inclusion in the CDF as part of TA491 (September 2017) and the end of the three-year CDF data collection period. The censoring date used was 29 March 2021, which matches the date used in the CDF three-year report.
- The study population was then selected using the CDF/Blueteq data held within PHE, using the same population involved in the analysis for the three-year report.
- This data was then linked using NHS numbers to the regimen data within SACT, with vital status data obtained from the National Cancer Registry Dataset for England.

Analyses

TTNT was defined as the time between when a patient starts treatment with ibrutinib and the time when this patient is switched to another regimen.

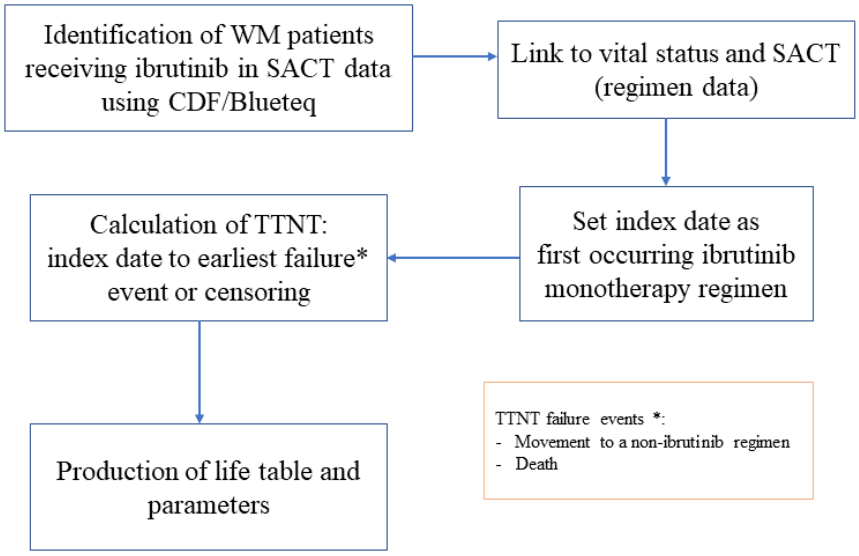
For the TTNT analysis, the time at risk is equal to the period in days between the index date and the date of earliest failure event or censoring:

- The index date was the date of ibrutinib monotherapy regimen documented for each patient.
- Failure events were defined as the earliest of movement to a new regimen or death.

The analyses were descriptive in nature, with no a priori hypotheses and no statistical tests conducted.

An outline of the process of patient identification and calculation of TTNT is presented in **Error! Reference source not found.** below.

Figure 1. SACT patient selection and data analysis



Results

Results for median TTNT and a Kaplan-Meier (KM) plot for TTNT are presented in the company technical engagement response document.

B. Incorporation of TTNT analyses in cost-effectiveness model

In order to incorporate the TTNT data within the economic model the following steps were undertaken:

1. Determining survival extrapolation for TTNT data

Patient-level data for TTNT were fitted with six standard parametric models. Fit statistics (AIC and BIC) and variance-covariance matrices have also been provided. The KM plot and parametric models are presented in XXXXXXX2, and the AIC and BIC fit statistics in Table 1.

AIC and BIC fit statistics indicated that the best fitting curve was the log logistic (Table 1). For AIC, the exponential reported fit statistics which was 6 units from the best fitting curve, while all other curves were within 5 units of the minimum AIC value. For the BIC, the generalised gamma statistic was > 5 units from the best fitting curve, with all other curves within 5 units of the minimum BIC value.

Table 1: AIC and BIC for parametric survival models fitted to time to next treatment from SACT

Model	AIC	BIC
Exponential	1743.94	1748.65
Generalised Gamma	1738.16	1752.30
Gompertz	1738.81	1748.23

Log-logistic	1737.77	1747.20
Log-normal	1740.41	1749.84
Weibull	1740.06	1749.48
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion. **Note:** Bold indicates the best-fitting model.		

Visual inspection of the fitted models indicated that, with the exception of Weibull, all the curves fitted the KM data well up to 30 months. The Weibull consistently underestimated TTNT data from 18 months onwards and was therefore excluded from further consideration. Of the remaining curves, the long-term predictions for the generalised gamma, Gompertz, log-logistic and lognormal were considered unrealistic, with between 6% and 25% of patient not having moved to next treatment at 30 years. Such projections lack clinical plausibility. Visually, the exponential curve fitted the data well and predicted 90% of patients having moved to next treatment at 10 years.

[redacted]

Therefore, on the basis of long-term plausibility, the exponential curve was considered the most clinically plausible option and was aligned with the distribution used to model SACT TD in the company CDF submission, thereby ensuring internal validity in the modelling.

2. Incorporating TTNT data into the economic model

Extrapolated TTNT data was then assumed to represent PFS for the SACT cohort within the economic model. PFS for physicians' choice was modelled using the same method as used in the revised company base-case, where PFS was derived using a treatment effect hazard applied to ibrutinib PFS (now modelled using SACT TTNT).

OS was recalibrated to fit OS KM data from SACT, using ordinary least squares regression, in line with the ERG approach.

Below is a summary of all assumptions used in this scenario analysis compared with revised company base-case (ERG preferred analysis) for extra clarity:

Table 2. Summary of assumptions for TTNT scenario (Scenario 1)

Model Input	New company base case	Scenario 1 – Revised company base case with ibrutinib PFS = TTNT
Ibrutinib PFS	PFS is calculated from HR obtained from exponential extrapolations of RMR TD and RMR PFS, applied to SACT TD as baseline.	PFS is calculated from parametric model fitted to TTNT data obtained from same SACT cohort as in SACT final report.
HR PFS for ibrutinib vs PC	Original FAD ITC HR.	As per the revised base case.
Ibrutinib PPM	SACT OTM fitted with parametric models.	As per the revised base case.
OS	OS calculated using PPS adjustment obtained from minimising sum of the squared errors between SACT OS KM and projected model OS.	As per the revised base case.

Key: FAD, Final Appraisal Determination; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival, OTM, on-treatment mortality; PFS, progression-free survival; PPM< post-progression mortality; SACT, Systemic anti-cancer therapy; TD, treatment duration; TTNT, time to next treatment.

Appendix 2 – PFS matched-adjusted indirect comparison

Given only aggregated data was available for Study 1118E long-term (59 months) follow-up, the update of the FAD ITC, which was based on 24-month follow-up data, was conducted using a matched-adjusted indirect comparison (MAIC).

A. Study compatibility assessment

The first step in performing a MAIC is to conduct a compatibility assessment through a review of the design and population profiles of the studies involved in the analyses. This section summarises key information from this review and highlights differences that present challenges or require specific assumptions in analyses.

At baseline, the key difference in design between the Study 1118E and the WM European Chart Review (ECR) were the following:

Number of prior lines of treatment
- 1118E inclusion criteria was subjects with relapsed/refractory (RR) WM
- ECR cohort included patients with any number of prior lines of treatment (0 to 5 lines)

Study type
- 1118E: (Phase II) single-arm, United States (US) multicenter study of ibrutinib
- ECR : observational chart review, physicians retrospectively completed in 10 EU countries

Follow-up
- 1118E: up to 60 months
- ECR : up to 120+ months

Region
- 1118E: US
- ECR : European Union.

Almost 50% of patients had missing data on one or more prognostic factors in ECR dataset.

Baseline characteristics of patients with complete baseline data on all prognostic factors are shown in

Table *3* below.

Table 3. Baseline Characteristics, Study 1118E vs. ECR

	ECR (R/R; Complete Data) N = 397	**Study 1118E (Per CSR) N = 63**
Age (< 65)	[redacted]	32 (50.8%)
Male	[redacted]	48 (76.2%)
Months since diagnosis (Mean)	[redacted]	90.3
IPSS Risk Score		
IPSS-WM Low	[redacted]	15 (23.8%)
IPSS-WM Intermediate	[redacted]	27 (42.9%)
IPSS-WM High	[redacted]	21 (33.3%)
Missing – n	[redacted]	
Serum IgM < 40 g/L	[redacted]	37 (58.7%)
Missing – n	[redacted]	
β2 microglobulin >3 mg/L	[redacted]	43 (68.3%)
Missing – n	[redacted]	
Hgb ≤ 110 g/L	[redacted]	38 (60.3%)
Missing – n		
Platelet ≤ 100 x 10^9/L	[redacted]	7 (11.1%)
Missing – n	[redacted]	
Number of previous regimens		
-1	[redacted]	18 (28.6)
-2	[redacted]	14 (22.2)
-3	[redacted]	8 (12.7)
-4+	[redacted]	23 (36.5)

Key: CSR: clinical study report; Hgb = haemoglobin; IPSS = International Prognostic Scoring System; R/R = relapsed or refractory; WM = Waldenström's macroglobulinemia

Key differences in patient populations were observed for IPSS-WM score and number of prior lines of treatment:

- Higher proportion of patients in Study 1118E were in IPSS lower risk score compared to ECR , i.e., 23.8% vs. [redacted], respectively.
- Patients enrolled in study 1118E were heavily pre-treated; 23 (36.5%) of patients received 4 or more regimens while in ECR only 12 ([redacted]) of patients had 4 or more prior regimens.
- Substantial number of missing value in β2 microglobulin and serum IgM in ECR leading to a high number of missing IPSS risk scores.

Though some differences in study designs (i.e., type of study, region, follow up time) cannot be adjusted for, other large imbalances in patient characteristics such as number of previous therapies or IPSS score could be adjusted with the MAIC method. Adjustment for these differences were expected to improve the efficacy outcomes of ibrutinib vs. Physician's Choice (PC) after MAIC adjustment compared to the naïve comparison.

B. List of variables for matching ECR to ibrutinib from study 1118E

The match was performed based on all available patient characteristics at baseline common to both studies.

i. Age
ii. Sex
iii. Serum β2-macroglobulin
iv. Hemoglobin
v. Serum monoclonal IgM
vi. Platelet count
vii. WM International Prognostic Score
viii. Time from WM diagnosis
ix. Prior lines of treatment (1, 2, 3, 4+).

Given the high imbalance in number of prior lines of treatment, matching on all characteristics significantly reduced the effective sample size (ESS). Number of prior lines of treatment was one of the main factors driving ESS down as its distribution had the smallest overlap between study 1118E and ECR.

C. Statistical methods

Published data on patient characteristics and outcomes from study 1118E on ibrutinib monotherapy and patient-level data for PC from the ECR study cohort (n=397) were used for analyses. Since almost 50% of the patient had missing data on at least one of the prognostic factors considered in MAIC matching, multiple imputation (MI) method was used to imputed 5 datasets of 397 and used in these analyses. Details on MI are provided in the section below.

Multiple imputation process for missing data

Given the extent of missing data in ECR where almost 50% of patients had missing at least one prognostic factor, a multiple imputation approach was implemented. Missing patient characteristics and prognostic factors in the mixed-line chart review cohort were imputed to

increase the sample size and the power of the analysis. The multiple imputation by chained equations (MICE) package in R was used to impute the missing data. MICE implements fully conditional specification (FCS) to impute missing data that occur in more than one variable. FCS specifies the multivariate imputation model on a variable-by-variable basis by a set of conditional densities, one for each incomplete variable. Starting from an initial imputation, FCS draws imputation by iterating over the conditional densities. All variables were imputed using a predictive mean matching method, and the output was visually assessed for convergence and whether the distribution of the imputed values matched the distribution of the original data. A total of five different plausible imputed data sets were generated.

Deriving virtual patient-level data for ibrutinib monotherapy

Engauge Digitizer was used to convert the image file of the PFS KM curve for ibrutinib from the 1118E trial into numbers with x and y coordinates (i.e., time and survival probabilities). To ensure accuracy, the digitized curves were overlaid on the original image and visually compared against the original curve. These coordinates were then used to generate virtual patient-level (VPL) data for each curve using methods described by Guyot ***et al***. The VPL data were checked for accuracy by plotting the resulting KM curves against the coordinates from the published graphs.

MAIC

The MAIC analysis followed the general steps described by Signorovitch ***et al.*** 2012 and involved four key steps:

1. Deriving balancing weights for each of the 5 imputed dataset
2. Applying the balancing weights to obtain adjusted outcome estimates for PC for each imputed dataset
3. Deriving comparative effect estimates for each imputed dataset
4. Deriving comparative effect estimate by pooling the comparative effect estimate of each imputed dataset.

These steps are described further below. Described steps below were repeated for each imputed dataset.

Deriving balancing weights

The MAIC technique relies on weights assigned to patients in the index trials (PC from the ECR study in this case) to balance differences in baseline characteristics with those of the comparator trial: ibrutinib from study 1118E. The weights were derived in such a way that the reweighted profile for each imputed dataset matches the population of the comparator study on all common characteristics without overmatching.

Weights were derived from a propensity score-type logistic regression equation that predicted whether a given type of patient originates from the index trial or the comparator trial as a function of baseline characteristics. More specifically, weights were given by the odds calculated by $w_i = exp(\alpha + x_i'\beta)$, where x_i' is the vector of baseline variables included for matching. The coefficients were determined by method of moments rather than maximum likelihood (as is usually the case) because only median values of the x's were available for the comparator populations.

Once the coefficients were estimated, the equation above was applied to calculate weights for each patient in the ECR Study arm. The weighted average of baseline characteristics for each imputed dataset was calculated and shown to compare to the target values from study 1118E.

The weights were also used to calculate the effective sample size (ESS) achieved after weighting patients. This was calculated by $(\sum w_i)^2/(\sum w_i^2)$. A low ESS may indicate an irregular distribution of weights across patients, meaning a small fraction of patients may be used to drive the treatment effect.

Deriving adjusted outcome estimates

Once the weights were obtained, they were applied to derive adjusted PFS.

A PFS-adjusted curve was obtained using the KM approach. The adjusted survival curve represented the expected outcomes of PC in a population matching study 1118E. The adjusted KM curve were plotted alongside the unadjusted PC curve and the observed curve from ibrutinib to illustrate the direction of adjustment.

Deriving estimates of relative effect

The relative effects on PFS of ibrutinib vs. PC was quantified as a hazard ratio (HR) with a 95% CI. The HR was obtained using a Cox regression analysis based on weighted patient-level data for PC and VPL data for ibrutinib.

A weighted Cox proportional hazards analysis was fitted to derive estimates of comparative effect on PFS. The Cox proportional hazards models included the indicator for treatment with ibrutinib vs. PC and applied weights derived in the previous step to balance the populations. The confidence interval for the hazard ratio estimate considered the ESS by normalizing the weights (w_i). VPL data for ibrutinib received weights of 1. A hazard ratio and 95% confidence interval were reported as an adjusted estimate of the relative effect.

Testing the proportional hazards assumption

To assess whether there was an indication of a violation of the proportional hazards (PH) assumption, plots of Schoenfeld residuals over log-time with a fitted penalized B-spline curve were generated and tests were performed for each of the treatment estimates from each of the imputed datasets. The mean p-value of all imputed datasets was calculated as an estimate of the PH test p-value for the pooled treatment effect estimate.

Additional details regarding the test can be found in the SAS Institute Inc. 2014. SAS/STAT® 13.2 User's Guide. Cary, NC: SAS Institute Inc. under the PHREG procedure "ZPH Diagnostics" section on page 5987.

Additionally, log-cumulative hazard plots were generated. Curves that are parallel suggest that the PH assumption holds; otherwise, more flexible methods such as time-varying Cox PH model might be more suitable.

D. MAIC results

Matching

Demographic and disease characteristics before and after matching between the ECR and the 1118E study are shown in Table 4. After matching, all baseline characteristics included in the matching were closely balanced between the two populations although some residual differences remained in IPSS and its components; the most important prognostic factor, number of previous regimens, was perfectly balanced in the MAIC.

Table 4. Demographic and disease characteristics before and after matching for PC from ECR vs. ibrutinib from study 1118E

	ECR N = 397	Study 1118E (Per CSR) N = 63	ECR after Adjustment Mean ESS: 84	
	Unadjusted proportions		MAIC Mean proportion	Matched on?
Age (< 65)	[redacted]	[redacted]	[redacted]	Yes
Male	[redacted]	[redacted]	[redacted]	Yes
Months since diagnosis (Mean)	[redacted]	[redacted]	[redacted]	Yes
IPSS Risk Factor				Yes
IPSSWM Low	[redacted]	[redacted]	[redacted]	
IPSSWM Intermediate	[redacted]	[redacted]	[redacted]	
IPSSWM High	[redacted]	[redacted]	[redacted]	
Serum IgM < 40 g/L	[redacted]	[redacted]	[redacted]	Yes
β2 microglobulin >3 mg/L	[redacted]	[redacted]	[redacted]	Yes
Hgb ≤ 110 g/L	[redacted]	[redacted]	[redacted]	Yes
Platelet ≤ 100 x 10^9/L	[redacted]	[redacted]	[redacted]	Yes
Number of previous regimens				Yes
-1	[redacted]	[redacted]	[redacted]	
-2	[redacted]	[redacted]	[redacted]	
-3	[redacted]	[redacted]	[redacted]	
-4+	[redacted]	[redacted]	[redacted]	

Key: CSR: clinical study report; ESS: effective sample size; Hgb: hemoglobin; IPSS: International Prognostic Scoring System; MAIC: matching-adjusted indirect comparison; R/R: relapsed or refractory; WM: Waldenström's macroglobulinemia

Progression-free Survival

In the MAIC, adjustment produced a shift downwards in the KM plot for ECR (weighted data, XXXXXXX3) after ~12.5 months. Before 12.5 months, there was no substantial difference between the unadjusted and adjusted data. The large change in the adjusted KM data was driven by the death/progression of two patients with the largest weights coupled with a small effective sample size (ESS). Results for the PFS MAIC are presented in Table 5 below:

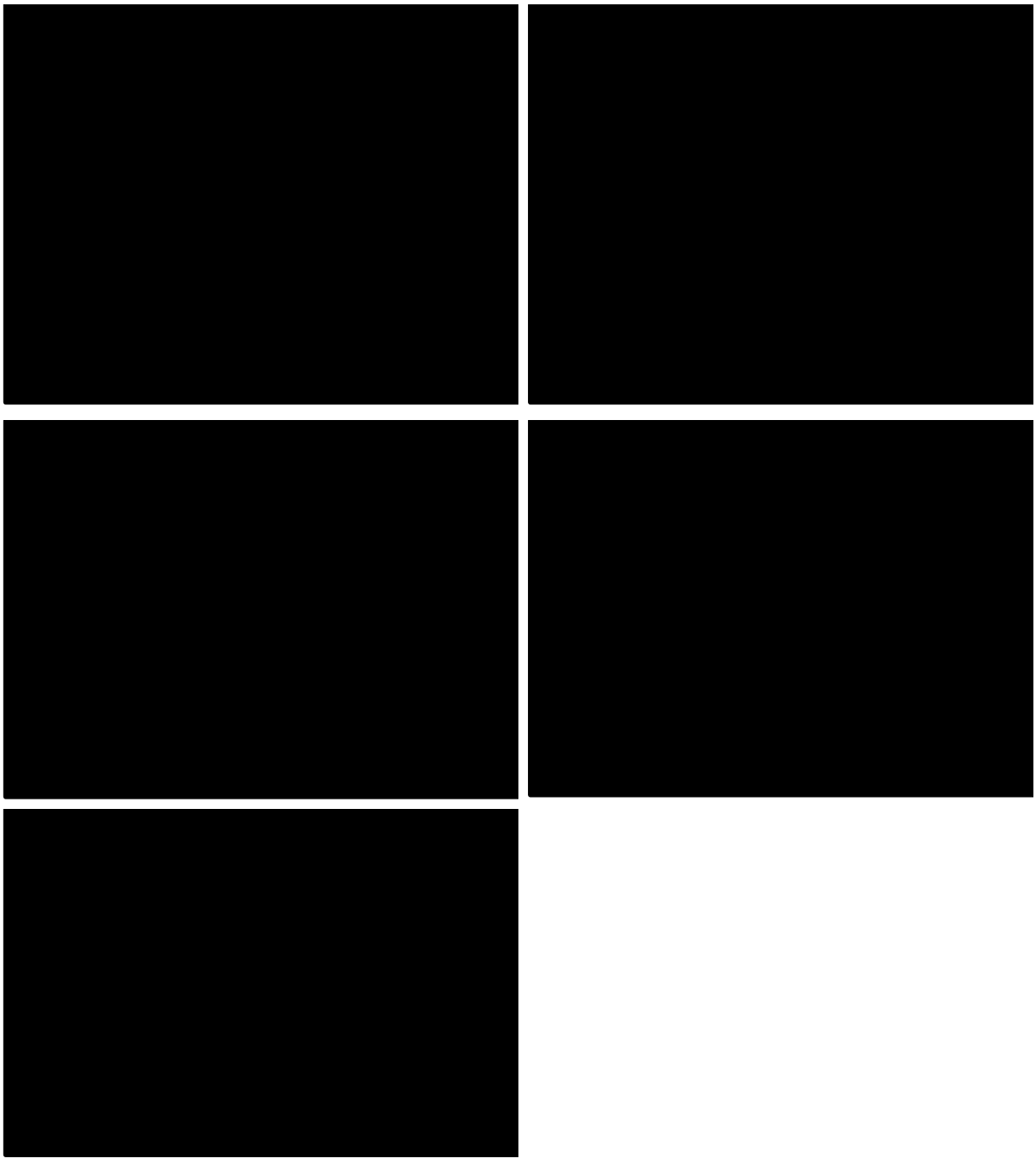
Table 5. MAIC results for PFS for ibrutinib vs. PC

	MAIC
Mean Effective sample size for ECR Study (Range)	84.4 (81, 91)
PFS Ibrutinib vs. PC HR (95% CI)	[redacted]

Key: CI: confidence interval; ECR: European chart review; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; PFS: Progression-free survival; PC: Physician's Choice; WM: Waldenström's macroglobulinemia

Hazard ratio <1 favors ibrutinib monotherapy.

3 [redacted]



Assessment of the proportional hazards assumption

Results of the PH assumption tests of the treatment effects from each of the imputed datasets are presented in Table 6 below. Plots of the weighted Schoenfeld residuals over log-time with a fitted penalized B-spline curve are in Figure 4. All individual p-values were > 0.05 which indicates that there is not enough evidence to reject the PH assumption in each of the imputed datasets, separately. Therefore, by combining the estimates from each imputed dataset, we also expect that the PH assumption holds for the pooled ibrutinib vs. PC PFS HR. Schoenfeld residual plots showed slight deviations from the PH assumption at early times where the two KM curves overlap and at the tail after ~4 log-months but the fitted B-spline curve is relatively flat between ~2 and ~4 log-months where most of the data are.

Additionally, log-cumulative hazards plots are shown in Figure 5. The trend over time is consistent with what was observed in the Schoenfeld residual plots in which curves are not parallel in first ~2 log-months (i.e. ~7 months). However, from 7 months and until the end of the 1118E follow-up at ~75 months the curves seem parallel which suggests that overall, the PH assumption holds.

Table 6. Proportional hazards assumption tests for each of the five imputed datasets

	P-value
Imputed Dataset #1	0.2550
Imputed Dataset #2	0.2714
Imputed Dataset #3	0.2818
Imputed Dataset #4	0.2117
Imputed Dataset #5	0.2161
Mean	0.2472

P-value < 0.05 suggests a violation of the proportional hazards assumption.

Figure 4.Schoenfeld residuals vs log-time plots of ibrutinib vs. PC PFS HR for each of the five imputed datasets

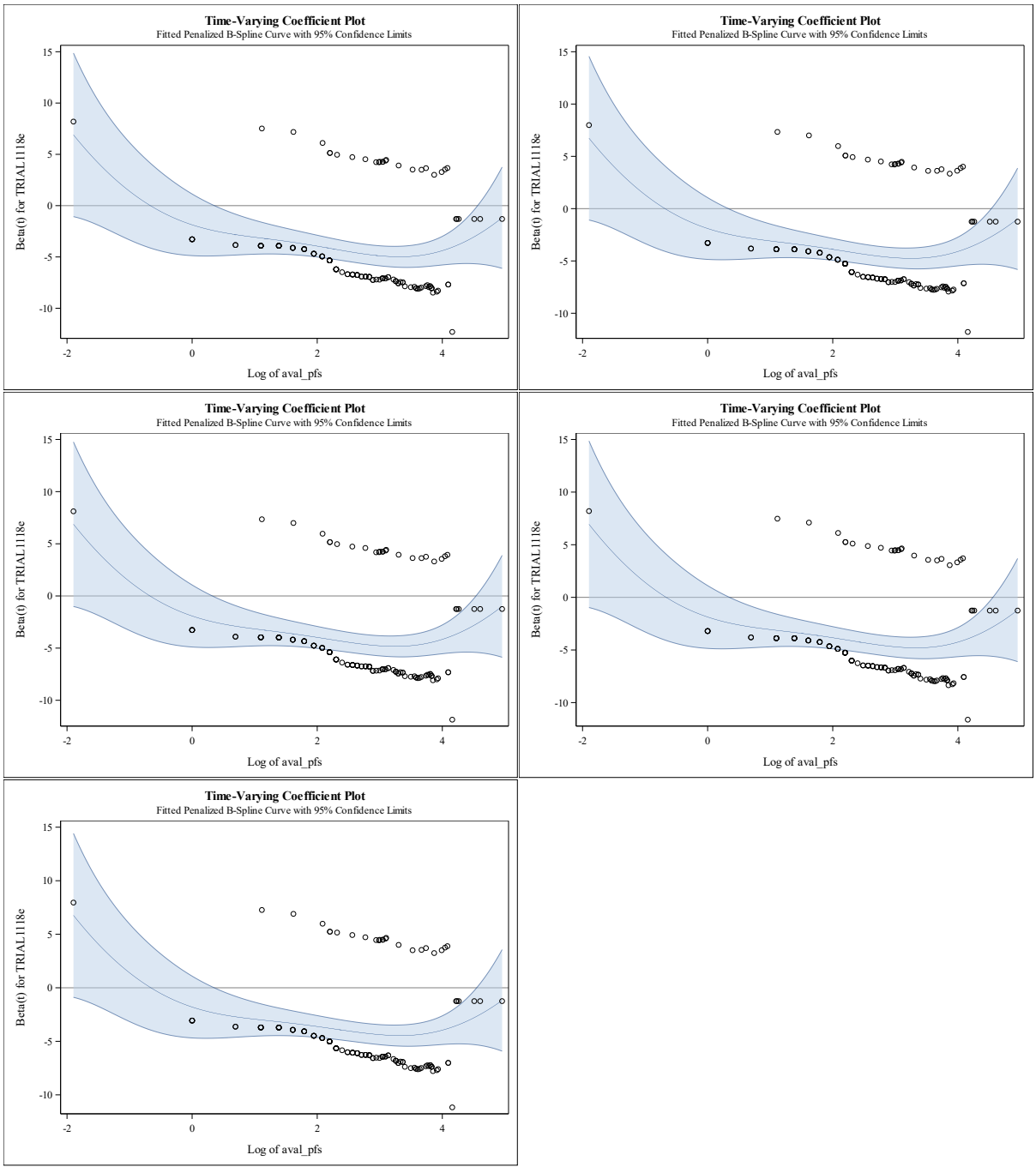
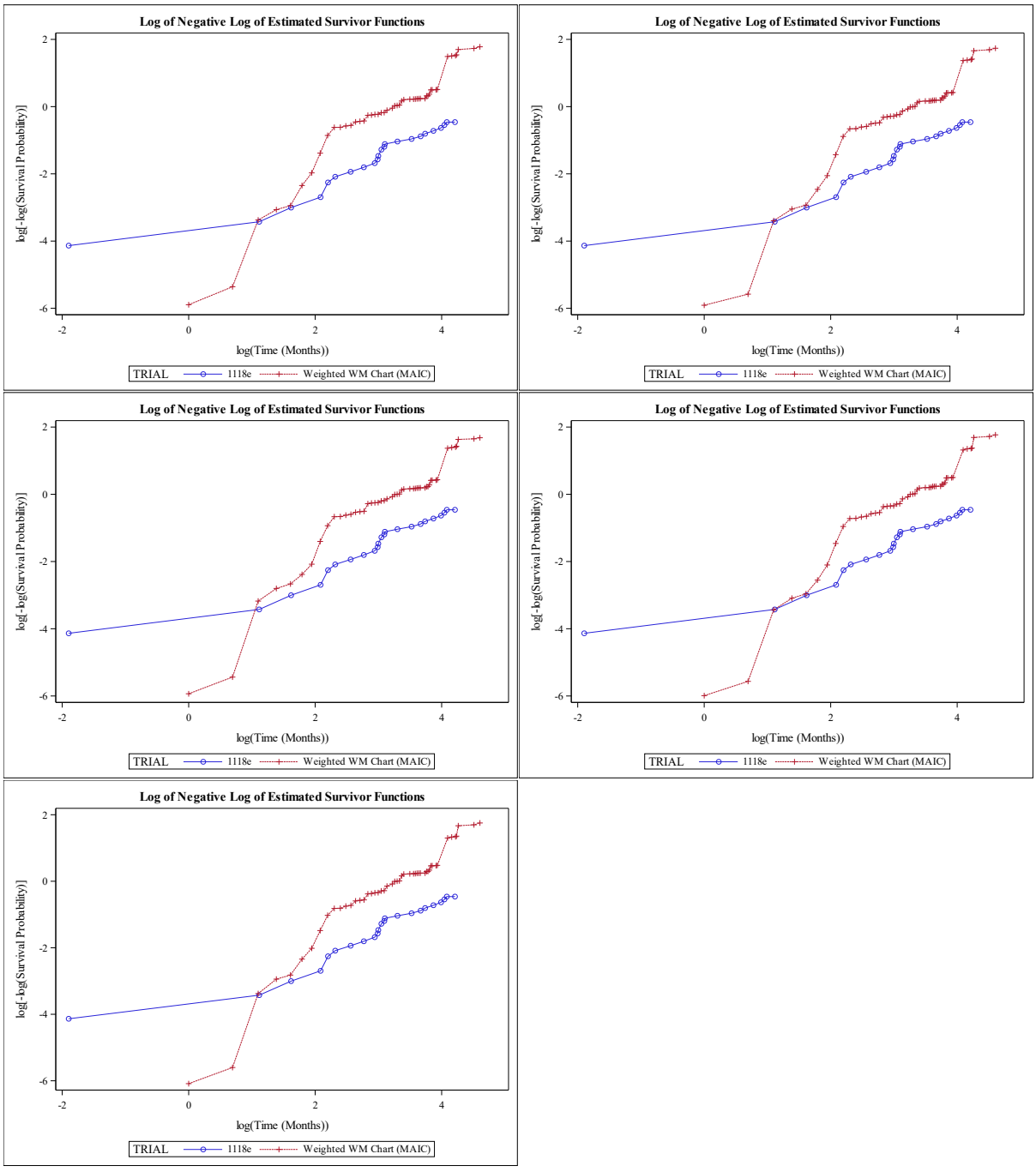


Figure 5. Log-cumulative survival vs log-time plots of ibrutinib vs. PC PFS for each of the five imputed datasets



E. Incorporation of MAIC analysis in cost-effectiveness model

The HR from the FAD ITC was updated with the MAIC HR in the revised company base-case. Below is a summary of all assumptions used in this scenario analysis compared with revised company base-case (ERG preferred analysis) for extra clarity:

Table 7.Summary of assumptions for MAIC scenario (Scenario2)

Model Input	New company base case	Scenario 2 – Revised company base case with MAIC
Ibrutinib PFS	PFS is calculated from HR obtained from exponential extrapolations of RMR TD and RMR PFS, applied to SACT TD as baseline.	As per the revised base case.
HR PFS for ibrutinib vs PC	Original FAD ITC HR.	Updated MAIC between Study 1118E PFS [59m] and the European Chart Review Study.
Ibrutinib PPM	SACT OTM fitted with parametric models.	As per the revised base case.
OS	OS calculated using PPS adjustment obtained from minimising sum of the squared errors between SACT OS KM and projected model OS.	As per the revised base case.
Key: FAD, Final Appraisal Determination; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival, OTM, on-treatment mortality; PFS, progression-free survival; PPM< post-progression mortality; SACT, Systemic anti-cancer therapy; TD, treatment duration		

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Clinical expert statement & technical engagement response form

Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of TA491) [ID3778]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

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- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 17 September 2021**

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Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with Waldenstrom's macroglobulinaemia and current treatment options	
About you	
1. Your name	**Dima El-Sharkawi**
2. Name of organisation	**Royal Marsden Hospital** Representing British society haematology and Royal College of Pathology
3. Job title or position	**Haemtology Consultant**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with Waldenstrom's macroglobulinaemia? ☒ a specialist in the clinical evidence base for Waldenstrom's macroglobulinaemia or technology? ☒ other (please specify): trustee of WMUK
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ I wrote the original submission for the stakeholders BSH and Royal College Pathologists
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**nil**
The aim of treatment for Waldenstrom's macroglobulinaemia	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**I have previously submitted this section and will just complete the TE part and have added to points 15 and 17**
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in Waldenstrom's macroglobulinaemia?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	

• What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful	

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The use of ibrutinib has become embedded in the treatment pathway off patients with WMUK, to not have it as a treatment option now would be a big step backwards. The majority of patients requiring therapy for relapsed/refractory disease who have not had a BTK inhibitor previously will now tend to be offered ibrutinib as a good treatment option with a different efficacy and toxicity profile.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This is reflected in the number of patients who were offered ibrutinib as SACT on the CDF being much higher than expected. I think this number would come down, and partly reflects the unmet need, but that all patients at every line of therapy would have potentially been considered for ibrutinib for their next line as they had not had it previously, whereas going forwards, I think it would tend to be offered 2nd and 3rd line.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Quality of life is very important and isn't always reflected in the clinical trials. I believe that quality of life is improved for patients on ibrutinib, and the speed of response which can also have an impact is improved by ibrutinib. Furthermore, even once progressed as defined by international criteria, the patient may stay on treatment for a period of time afterwards as there may be no indication to immediately change treatment.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes given that the only current standard therapies are chemoimmunotherapies.
• Does the use of the technology address any particular unmet need of the patient population?	Yes this gives an option for those who are unsuitable for chemoimmunotherapy and helps to reduce the need for repeated lines of chemoimmunotherapy which will increase potential long term toxicity.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 491.	

23. How do data on real-world experience compare with the trial data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issue 1: The evidence used to inform the company's CDF model remains highly uncertain	Realistically, data is not going to have significantly changed in 4 years since ibrutinib has been accessed through the CDF, WM is a fairly indolent disease on the most part and thus as has been seen, even in the phase 2 trial by Treon et al, and the updated follow up that has now been presented (JCO 2020) that median PFS has not been reached at 5 years, and so it is too early for us to be able to really analyse the data in the RMR and also follow on data once disease has progressed. As mentioned previously, many patients with WM will die of other causes rather than WM directly, this has an impact on expected survival data that adds complexity to the modelling. To further add complexity, the other causes of death may be partly due to completely unrelated causes eg. Comorbidities, but some will be indirectly related to WM either due to complications and risks of the disease itself e.g. infection risk or due to the toxicity of the therapy e.g. secondary MDS due to repeated chemoimmunotherapy. Finally, I do not think that trial readouts and PFS are particularly useful in the real world setting and do not reflect clinical practice which also adds difficult in extrapolating from trial reads out to model predictions.

Issue 2: The company's model predictions of health state occupancy are not plausible	In terms of clinical modelling this is what I would propose: **Chemoimmunotherapy:** Patient requires and has chemoimmunotherapy for defined time. Patient treatment free and "disease has responded" Patient progresses (as defined by international criteria) but not requiring therapy Patient requires next line of therapy. There may be a significant lag between the time point that the patient progresses as defined by international criteria and the time point that the patient actually requires therapy. **Ibrutinib:** Patient requires therapy and commences ibrutinib Time to response likely to be shorter than chemoimmunotherapy Patient continues therapy and "disease has responded" Patient progresses (as defined by international criteria and this is the timepoint that would be read out in clinical trials but is still on therapy at this point and is still getting clinical benefit and thus would continue on ibrutinib Patient requires next line of therapy. (Very few patients will stop ibrutinib before progressing due to intolerance, and I would estimate 5-10%) Thus I do find that the models not reflective of clinical practice as patients would not have a lag between stopping ibrutinib and progressing as they would progress whilst on ibrutinib and there would be a period

	of time when potentially they remain on ibrutinib because of ongoing clinical benefit and no indication for next line of therapy but in technically the progressed state. Following the use of ibrutinib, I think the time between progression and death is not realistic, as I would expect a lot longer median time. The majority of patients who progress following ibrutinib and who require next line of therapy, would be considered for further treatment with either clinical trials or further chemoimmunotherapy. As can be seen from the Rory Morrison registry and published realworld data, patients can still achieve good responses with repeated lines of chemoimmunotherapy although duration of response may shorten compared to first line. There is little data to show responses to chemoimmunotherapy following ibrutinib due to the short follow up time, but there is no reason to suspect that the ibrutinib would significantly alter the outcome compared to having chemoimmunotherapy 2nd or 3rd line. I also believe that the estimation of people alive after 6 years following "physician's choice" of treatment is not clinically plausible. I think more people will be alive at this time point. The evidence to support this is from the expected survival seen in the RMR, and also other real world data such as by Buske et al (lancet Haematology 2018 5: e299-e309), this demonstrated in a large European chart review, that patients having second line chemoimmunotherapy, median PFS was approximately 23 months and 16 months at 3rd line, and as previously discussed, patients may not need treatment immediately after progression.
Are there any important issues that have been missed in ERG report?	As above, I believe that patients may technically progress but still be on ibrutinib and deriving benefit. The trial endpoints are not necessarily reflective of how we manage patients in the realworld. The trial endpoints do not reflect the benefit to quality of life as well as PFS enjoyed by many patients on ibrutinib.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Ibrutinib is a step wise change in the treatment of WM and to stop having it as an option for R/R WM would be a step back
- The trial endpoints do not reflect every day practice, due to the nature of the disease, there may be a significant lag between PFS and Time to next treatment.
- The trials do not reflect the quality of life gains that patients on ibrutinib can enjoy
- Realistically 4 years is too short a time to get a lot of extra data on the benefits of ibrutinib due to the rarity of the disease and the indolent nature of the disease that many patients experience.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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Clinical expert statement & technical engagement response form

Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of TA491) [ID3778]

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NICE National Institute for Health and Care Excellence

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with Waldenstrom's macroglobulinaemia and current treatment options	
About you	
1. Your name	**Shirley D'Sa**
2. Name of organisation	**UCLH NHS Foundation Trust, WMUK Charity**
3. Job title or position	**Consultant Haematologist and Associate Professor**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with Waldenstrom's macroglobulinaemia? ☐ a specialist in the clinical evidence base for Waldenstrom's macroglobulinaemia or technology? ☒ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**
The aim of treatment for Waldenstrom's macroglobulinaemia	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to treat disease progression with the aim of improving QOL and prolonging life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	There are published criteria for response to treatment, which are used in clinical trials, but in real world practice, a clinically meaningful response comprises more that the categorical responses such as CR, PR, etc. Improvement in well-being is frequently noted and in a rapid way- often within days due to an upturn in haemoglobin (correction of anaemia) and typically accompanied by a fall in paraprotein. This can be clinically meaningful even when a minor response is seen by paraprotein criteria, which is extremely valuable for patients. Close attention is

or a reduction in disease activity by a certain amount.)	paid to any adverse events which are then addressed appropriately. If stability is maintained along with well being then treatment is continued.
10. In your view, is there an unmet need for patients and healthcare professionals in Waldenstrom's macroglobulinaemia?	Yes, undoubtedly. Patients with WM inevitably become chemo refractory. During the process of multiple lines of therapy, they experience progressive immunological decline and an increasing number of opportunistic infections which can lead to an early treatment-related death. The possibility of using a targeted therapies such as Ibrutinib provides a lifeline for many of these patients when used judiciously in the treatment pathway.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Currently patients receive chemotherapy such as cyclophosphamide or bendamustine in conjunction with rituximab full six cycles spanning four to six months. These treatments are likely to induce a deep enough response to result in clinical stability and control of the disease with improvement in well being and a period of remission that may last anywhere between two and six years. In my experience the median is four or five years. Following inevitable disease progression, second line therapy comprises further chemo-rituximab regimens possibly including high dose chemotherapy and autologous stem cell transplantation getting a minority of younger fitter patients in order to achieve a second remission. Since 2017, Ibrutinib has been used via the CDF and has proved to be a favoured choice for many clinicians and patients due to quick responses, rapid improvements in well being and durable remissions. Some patients progress on Ibrutinib and have demonstrated a response to subsequent chemo immunotherapy. This appears more likely in those who have received fewer prior lines before Ibrutinib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are both British and international guidelines for WM. The latest British guidelines are being reviewed by the British society for haematology with a view to publication later this year. as an author of these guidelines I can confirm that ibrutinib is deemed to have an important role in the treatment of WM coma ongoing trials are aimed at understanding the most appropriate sequencing and possible combination with retuximab. There are also NCCN guidelines from the United States and international guidelines from the International WM Workshops (IWWM).

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care pathway is well defined in terms of lines of therapy. Within the NHS chemo immunotherapy is accepted as most appropriate first line therapy due to its effectiveness. There is widespread expectation among clinicians that chemorefractoriness will occur overtime and an agent like ibrutinib plays an important role at this point. it is widely employed at first relapse and beyond depending on the agent performance status of the patient. The sequencing of therapies is not clear cut in WM. This depends on patient related factors as well as disease characteristics including genetic expression of certain mutations. Strenuous efforts are being made to improve our understanding of this through clinical trials as well as real world data collection.
• What impact would the technology have on the current pathway of care?	This treatment has already demonstrated enormous benefit for patients who have failed multiple prior lines of therapy. It is also provided an important option for those in whom further chemo immunotherapy would be harmful do too poor performance status. I believe it is well placed in the relapse setting as an alternative option to chemo immunotherapy. There may be patients who would benefit from front line therapy with Ibrutinib but I have no personal experience of this as it is not available on the NHS as things stand.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, my expectation is that its use will be the same as it is currently employed in the NHS on the CDF
• How does healthcare resource use differ between the technology and current care?	This is the subject of ongoing studies both in the trial and real-world settings. Being an oral agent, there are immediate benefits for patients who can take the medication at home and once stabilised on it can visit the outpatient department every three months for review and further supply. This is in contrast to chemo immunotherapy where the current regimens are given intravenously and required day care attendance. This drug would be taken continuously until it no longer works whereas chemo immunotherapy is given for a fixed duration and then stopped. In terms of hospital attendance, the prescription of this technology does not significantly increase workload compared to intravenous therapies.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The appropriate clinical setting for this treatment is a specialist clinic in secondary care or tertiary care. the typical clinic where these patients are treated is a haematology clinic headed by a consultant haematologist and supported by a multidisciplinary team. Such arrangements are already in place.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The technology is already well established in the UK in this indication as well as others (CLL, Mantle cell lymphoma) and there is a wealth of experience in optimising the management of this drug even in the face of adverse events. Therefore I do not anticipate further investment in the introduction of this technology. In fact it is likely to reduce the need for special training for chemotherapy nurses which is needed for the administration of intravenous chemotherapy.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Definitely. I do not believe it will take the place of current therapies but will put an important adjunct to those therapies. we have witnessed clinically meaningful benefits in many patients at different stages of their treatment journey. For the most part tolerance of this treatment is extremely good. Intolerance can be managed in most cases by dose adjustment.
• Do you expect the technology to increase length of life more than current care?	By adding this technology into the current therapeutic armamentarium, I do believe that this technology will increase the length of life compared to its absence.
• Do you expect the technology to increase health-related quality of life more than current care?	This treatment has definitely improved health related quality of life more than current chemotherapy options for numerous patients. This has been observed from real-world data collection as well as patient focus groups and social media platforms. its availability as a second line option has been invaluable as its mode of action is very different to chemo immunotherapy. This provides a challenge to the disease and also limits the depth of immunosuppression seen when when chemoimmunotherapy is repeatedly used.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This therapy will be particularly useful in those who are poorly tolerant of chemo immunotherapy options. it also reduces regular visits to the hospital which is particular advantage in the COVID era. It may be less effective or appropriate in people who cannot comply with regular oral medication but such patients are relatively few in number.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This therapy is straight forward to administer. Experience gained from its use in this and other settings over the past few years have led to clear pathways for prescription and administration as well as supportive medications such as antibiotics and antiviral treatment. There are clear protocols for cessation of this treatment prior to interventions due to the bleeding risk on in reality this does not pose particular difficulties to the treating team or the patient. For most patients on chemo immunotherapy similar precautions are needed so this technology does not produce additional challenges in this regard.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Yes there are well developed starting and stopping criteria which are detailed in guidelines and also embedded in experienced clinical practice.

Do these include any additional testing?	Evidence for disease progression such as increasing disease-related symptoms such as progressive anaemia or other cytopenias, fatigue, weight loss, sweats, paraprotein-related symptoms such as IgM-mediated problems such as hyperviscosity unrelenting over time would indicate the need for starting treatment. This would generally be predicated by an examination of the bone marrow and CT scanning as per standard of care. Failure of the disease-related symptoms to relent, or recurrence of such symptoms after initial evidence of response and a rise in the paraprotein or would indicate a failure of response. This would be observed for consecutive readings over 1-2 months (cycles) leading to cessation of treatment. Continuation of futile therapy would not occur as this is contrary to specialist training the doctors receive and further develop in their daily clinical work. Apart from blood tests and serial recording of clinical features, a decision may be taken to repeat the bone marrow biopsy and CT scans to examine the extent of the burden of disease. This is part of standard of care and would not be unique to the use of this technology
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Most definitely. I believe that the QALY does not do justice to diseases such as WM, despite its obvious merits in assessment of health-related benefits. WM is a rare disease, symptoms are often non-specific and individual but clinically impactful for patients. Successful treatment of the disease clearly leads to improvements in QOL for patients. This is something I have observed in my clinical practice and through patient testimony. Improtantly, such improvements enable patients to return to activities that were previously beyond reach, including ADLs, employment and caring for dependents. I urge the committee to take account of the patient testimonies provided by WMUK as they capture information that is not captured elsewhere- details that show the difference that Ibrutinib makes in their lives.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes- the mechanism of action of Ibrutinib provides a completely different approach to treating WM, compared to traditionally applied chemoimmunotherapy. Used as part of the therapeutic arsenal, this technology makes a massive impact on health-related benefits and helps to prolong life.
• Is the technology a 'step-change' in the management of the condition?	Yes, by virtue of its targeting of critical B cell pathways, it enables a 'smarter' approach to treating WM, also taking account of genetic subgroups within the disease (using MYD88 and CXCR4 mutational status). With ongoing follow up of previous and current studies we will move towards a personalised approach to managing the disease, compared to the hammer-to-crack-a-nut approach provided by chemoimmunotherapy.
• Does the use of the technology address any particular unmet need of the patient population?	Yes- it enables more sophisticated management of the condition by offering the chance to match therapy to performance status – something that is less possible with chemoimmunotherapy. It enables patients to be more independent as they receive treatment, obviating the need to attend for intravenous chemoimmunotherapy.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ample experience has been gained and published around the adverse events that may occur and physicians are well aware of how to manage these. They include increased bleeding risk that is significant when patients are already receiving blood thinners for other conditions- these are adjusted as needed and the patient monitored for clinically significant events. The technology is paused prior to invasive procedures such as dental extractions, surgery and biopsies and then resumed thereafter.

	Cardiac arrhythmias are a recognised side effect which can be managed in most cases by rate controlling drugs or minimally invasive procedures such as ablation that are widely employed in Cardiology settings. A few patients experience GI upset (diarrhoea) or abnormalities in liver function tests. There is published guidance regarding dose adjustment in these circumstances. If the symptoms were pervasive despite this, the treatment would be stopped.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, to the extent that the technology is used in the relapsed/refractory setting in UK practice currently.
• If not, how could the results be extrapolated to the UK setting?	The real world data from the RMR shows some differences compared to the clinical trial settings but they broadly reflect clinical trial experience. This goes some way to providing extrapolative data for the UK setting.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are symptomatic clinical benefit with evidence of improvements in disease parameters. In the study by Treon et al (NEJM 2015), overall response rate and major response rate were notable. The median time to at least a minor response (1 month) is also significant as this can translate into rapid clinical benefit for patients. Overall survival is more difficult to interpret as patients do receive other therapies post-ibrutinib which contribute to the OS.
• If surrogate outcome measures were used, do they adequately predict	It is important to note that the kinetics of clinical response to treatment in WM can be at variance to measured response criteria as the fall in IgM may be slow in the face of clinical improvement. Surrogate outcomes depend to a certain extent on the goals of therapy in each patient. In an older, frailer patient, the goals of therapy may be more

long-term clinical outcomes?	focused on clinical improvement and not prolongation of survival. In others, it is lengthening of life is the main aim. The use of PFS as a surrogate endpoint in this setting has limitations; time to next treatment may be more representative. However, I am not a statistician and will therefore not offer further comment.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The development of hypertension in the 1-2 years following start of therapy is a more recent observation – one which can be effectively managed with simple measures- commencing antihypertensives as appropriate.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Below are pasted some new references that are of relevance Joshua N. Gustine, Shayna Sarosiek, Catherine A. Flynn, Kirsten Meid, Carly Leventoff, Timothy White, Maria Luisa Guerrera, Lian Xu, Amanda Kofides, Nicholas Tsakmaklis, Manit Munshi, Maria Demos, Christopher J. Patterson, Xia Liu, Guang Yang, Zachary R. Hunter, Andrew R. Branagan, Steven P. Treon, and Jorge J. Castillo. Natural history of Waldenström macroglobulinemia following acquired resistance to ibrutinib monotherapy. Haematologica. 2021; 106:xxx doi:10.3324/haematol.2021.279112 Shayna Sarosiek, Steven P. Treon & Jorge J. Castillo (2021): Reducing treatment toxicity in Waldenström macroglobulinemia, Expert Opinion on Drug Safety, DOI:10.1080/14740338.2021.1897565
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	Below are pasted some new references that are of relevance Judith Trotman et al. Single-Agent Ibrutinib for Rituximab-Refractory Waldenström's Macroglobulinemia: Final Analysis of the Substudy of the Phase III iNNOVATE TM TrialClin Cancer Res. 2021 Aug 11; clincanres.1497.2021. doi: 10.1158/1078-0432.CCR-21-1497.

of NICE technology appraisal guidance 491.	Shayna Sarosiek, Steven P. Treon & Jorge J. Castillo. How to Sequence Therapies in Waldenström Macroglobulinemia. Curr Treat Options Oncol. 2021 Aug 23;22(10):92. doi: 10.1007/s11864-021-00890-9.
23. How do data on real-world experience compare with the trial data?	Please find attached draft RMR 2021 Report which is confidential until published.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	NA

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issue 1: The evidence used to inform the company's CDF model remains highly uncertain	There are flaws in the model that are unavoidable given the limited trial data that are available, but I believe it has its merits. The different data sources provide similar but different data points which is unavoidable. I note the alternative approach suggested by the ERG but do not feel qualified to comment on the statistical modelling in detail.
Issue 2: The company's model predictions of health state occupancy are not plausible	(a) Ibrutinib group: The model suggests a large gap between TTD and PFS. This gap suggests that patients experience a mean lag of 1.18 years between the time at which they discontinue treatment with ibrutinib and the time at which they progress. The ERG's clinical advisor stated that patients are generally treated until progression and that those who discontinue before progression will progress after only a short period of time. -> I agree with the clinical advisor. (b) Ibrutinib group: The model suggests only a small gap between PFS and OS in the ibrutinib group. This suggests that patients treated with ibrutinib spend almost all of their survival time without disease progression. The ERG's clinical advisor did not consider this to be plausible and noted that patients who progress on ibrutinib are sometimes salvageable on 3L and 4L chemotherapy.

	-> I agree with the clinical advisor. (c) PC group: The model predicts that virtually all PC-treated patients (99.6%) will have died after around 6 years after starting initial treatment for R/R WM. The ERG's clinical advisor believed this was unrealistic as some patients survive beyond 6 years. -> I agree with the clinical advisor.
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Ibrutinib offers a game-changing opportunity in this disease, the benefits of which are apparent above and beyond the data emanating from the analysed data.
- It would be unthinkable to go back to a therapeutic world without Ibrutinib: the clinical benefit to patients that I have observed over the past 3+ years cannot be overstated.
- Ibrutinib is not a panacea, it is not a perfect drug but it addresses an unmet need like no other agent currently available for WM. I believe that clarity regarding starting and stopping criteria would help to maximise appropriate use and value for money.
- We are committed to continuing to collect ongoing real world via the RMR with the intention of providing greater clarity regarding the most appropriate sequencing of agents including Ibrutinib in WM

NICE National Institute for Health and Care Excellence

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of TA491) [ID3778]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on Thursday 16th September 2021

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with Waldenstrom's macroglobulinaemia and current treatment options	
About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with Waldenstrom's macroglobulinaemia? ☒ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with Waldenstrom's macroglobulinaemia? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	**WMUK**
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement and was not able to attend the expert engagement teleconference
Living with the condition	
6. What is your experience of living with Waldenstrom's macroglobulinaemia? If you are a carer (for someone with Waldenstrom's macroglobulinaemia) please share your experience of caring for them.	I was diagnosed with WM in November 2007. At the time it was a bombshell to myself and my family. It was a devastating life-changing moment. I was at the time the Senior Partner in a successful law firm in Grimsby. I was a Family/ Care cases and criminal defence Duty Solicitor which involved quite often working extremely unsociable hours, for example getting up in the early hours to attend to clients in the local police cells and Saturday and Bank holiday courts. This in addition to being expected to open the office post in the morning and deal with staff and office running meant I tended to work at 100 mph most days. I thought nothing of a 14-hour day. I used to run up and down my office stairs 2 steps at a time and the same in the court building without putting on a sweat. Out of the office I had as busy a family life as I could with a wife and two children- we would spend time in the Lake District, the Yorkshire Dales and Derbyshire walking and enjoying the scenery if not abroad.

	However, in 2007 I thought I had a prostate problem. I had the usual investigations and was told I didn't have a problem, but my GP noticed something in my blood results, and I agreed to see haematology and have a bone marrow done. I still carried on as normal until I was told I had WM. Realising I had cancer, whilst a shock, made the decision for me to begin to take stock of my life and retire very early in 2009 at the age of 54. I was on watch and wait from then and my wife and I moved to our house in Cyprus to enjoy our retirement together. I had noticed whilst at work that I was sweating and struggling with getting upstairs as I used to and clearly fatigue was at play. I took life more slowly but realised it was only a matter of time before chemotherapy would be needed. By 2014 we returned to live in the UK, and I began R-CVP in January 2015 - I found this hard and draining. I had 4 cycles that ended on 13/3/2015. Seemingly my readings had improved so as not to necessitate the 5th & 6th cycles. My paraprotein was up to 21.4 at the beginning but down slightly to 16.9 in the February. My readings continued on an upward trajectory when a second round of chemotherapy DRC began - I was due for 6 cycles that began on 13/3/2017 - I lost consciousness on the second cycle and had to be resuscitated and the cycle was aborted. The third cycle took place on 2/5/2017 but again despite slowing down the rate of absorption I had peculiar sensations in my arms and chest and so that too was aborted. I had no more chemotherapy from that point in time and back to watch & wait.

	My paraprotein level did drop into the mid-teens but began creeping back up through the rest of 2017,2018, and 2019 reaching 22.3 by August and by early September I had started Ibrutinib. My reading in early October was 16 and by late October 6.9 and in late November it was 3.8. This represented a huge improvement in my wellbeing and gave me a quality of life that I had lost since chemotherapy began in 2015. At this time due to osteoarthritis in both hips and severe pain and an inability to walk any real distance my haematologist stopped my ibrutinib as we wondered whether the joint pain was due the Ibrutinib itself. My January 2020 paraprotein reading was 32. The highest it's ever been. I had been off Ibrutinib for about 6 weeks. It was reinstated at the end of January and by 6/2/2020 the paraprotein was down to 8. This showed that my body clearly needs the drug to keep me well and that it works very quickly. By June it was <2.4 - this represents a complete shift in my ability to function normally. In September 2020 I had a right hip replacement operation and in March 2021 I had a left hip replacement operation. My surgeon Mr Omanbude well knew from my medical records and how well Ibrutinib was doing for me but he insisted I stop the drug for 5 days before each operation. I have to say that after 24 hours of not taking Ibrutinib I looked and felt like my "old drug taking clients", I was doing cold turkey and felt really poorly and wondered if they would let me have the surgery I desperately needed. My surgeon has told me that he is happy to confirm my presentation in theatre as I was apparently "sweating profusely" during the operations but he allowed me to resume Ibrutinib immediately I came round from

	the anaesthetic. I am very glad he did as I returned to my state of well-being almost immediately. As of today, my paraprotein remains at <2.4 and my haemoglobin is 146 - the latter has not been this normal until the introduction of Ibrutinib where it has grown in strength to this normal level. Prior to Ibrutinib my haemoglobin level was very low in the 80s -90s - so it has massively helped my quality of life and what I can now do that I couldn't pre - Ibrutinib. Prior to going onto Ibrutinib I had several iron infusions and a blood transfusion. Needless to say, the worry my wife and family had because of my WM was immense- now we are all much more positive for my future outlook. During my WM journey and due to my mobility issues my wife has become my official carer and she has shared the extreme worry over the years due to my WM being incurable but now we both feel I have an effective treatment that is giving us hope that I can survive WM and enjoy life again.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for Waldenstrom's macroglobulinaemia on the NHS?	Personally, chemotherapy does not work to any significant degree, whereas Ibrutinib clearly does and gives me a real quality of life and purpose.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Not aware.
8. If there are disadvantages for patients of **current NHS treatments** for Waldenstrom's macroglobulinaemia (for example how ibrutinib is given or taken, side effects of treatment etc) please describe these	Disadvantage of chemotherapy is the length of time a patient has to sit in a hospital chair day after day cycle after cycle, hour after hour plus it doesn't provide an effective lasting treatment unlike Ibrutinib. The side effects of Ibrutinib for me have been occasional mouth ulcers, skin rashes and I easily bleed - however they are worth putting up with so long as I continue to receive the targeted drug Ibrutinib. The cost advantages of Ibrutinib taken orally at home once a day to the cost of chemotherapy delivered in several cycles over several weeks/ months tying up Hospital resources is surely a no brainer!
Advantages of this treatment	
9a. If there are advantages of ibrutinib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	Ibrutinib is taken orally at home or wherever you want - e.g. I took 14 days+ supply on our recent holiday abroad. Chemotherapy is delivered at hospital on a day unit and takes hours and the valuable time of nurses and other staff is taken up. The advantages of Ibrutinib are overwhelming and positive in vastly improving my quality of life. 9b. – Quality of life improvements 9c. – Yes, see 8 above.

9c. Does ibrutinib help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of ibrutinib over current treatments on the NHS please describe these? For example, are there any risks with ibrutinib? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	I have been on Ibrutinib for 2 years and I can say there are no disadvantages of Ibrutinib over current treatments (chemotherapy etc) I have no concerns about using Ibrutinib and hope to be a long-term user of it via the NHS hopefully.
Patient population	
11. Are there any groups of patients who might benefit more from ibrutinib or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Clearly WM affects the older population, and they tend to have mobility issues (as I have) and so the convenience of taking a tablet at home thereby avoiding the need to get to a hospital to have a cannula put in their arm with all associated transport and logistic issues. This demonstrates how beneficial it is to use a daily targeted drug like Ibrutinib.

Equality	
12. Are there any potential equality issues that should be taken into account when considering Waldenstrom's macroglobulinaemia and ibrutinib? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	I'm not able to comment save to say that I would hope anyone likely to benefit from using Ibrutinib should be allowed to.

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Chemotherapy provided short term remissions and has had very significant side effects for me which meant I could not tolerate the regimens.
- Ibrutinib has provided me with a quality of life I didn't know was possible after going through chemotherapy twice and I regard it as a life transforming drug.
- Ibrutinib worked very quickly on my WM symptoms and when paused symptoms came back also quickly - this proves to me it's efficacy.
- Ibrutinib is a highly effective targeted drug in my case and has met an unmet need being highly effective compared to chemotherapy which did not succeed in my case and so has proved clinically effective and hopefully proves to be cost effective too.
- Ibrutinib taken orally at home daily particularly in these COVID 19 times we are stuck with for some time to come, has a massive advantage over trying to get us elderly patients into hospital thereby saving countless thousands of outpatient appointments all over the country.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Ibrutinib for Waldenström's macroglobulinaemia: A Cancer Drugs Fund review

Addendum: ERG comments on the company's technical engagement response

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1. Introduction

In September 2021, the company submitted their technical engagement (TE) response to the National Institute for Health and Care Excellence (NICE). The company's TE response includes a written response document[1] with accompanying appendices[2] and an updated executable model. Statements from two clinical experts were also submitted to NICE.[3, 4] This addendum provides a brief critique of the company's TE response.

2. Summary of company's TE response and additional analyses

The company's TE response is summarised briefly below.

Issue 1: The evidence used to inform the company's CDF model remains highly uncertain

The company's TE response[1] acknowledges that the ERG's preferred approach to estimating progression-free survival (PFS) has greater face validity than the company's original approach. The company's response states that the company's base case has been amended in line with the ERG's preferred analysis. This increases the company's original base case incremental cost-effectiveness ratio (ICER) from [redacted] to [redacted] per quality-adjusted life year (QALY) gained.

The company's TE response[1] includes an additional analysis of time to next treatment (TTNT) data from the same cohort of the Systemic Anti-Cancer Therapy (SACT) dataset[5] which is used in the company's model. The company's response presents the results of a scenario analysis using their updated base case model whereby PFS is assumed to be equal to TTNT, based on an exponential survival distribution. This analysis leads to an ICER of [redacted] per QALY gained. The company's response states that TTNT represents an upper bound for PFS and that the true PFS in the SACT cohort is likely to lie between time to treatment discontinuation (TTD) and TTNT.

The company's TE response[1] also includes an updated indirect treatment comparison (ITC) which takes the form of an unanchored matching-adjusted indirect comparison (MAIC) using the 59-month data-cut from Study 1118E[6] and the full dataset from the European Chart Review (ECR).[7] A detailed description of the MAIC is provided in the appendix to the company's TE response document.[2] The MAIC included matching on the same characteristics as those used in the ITC contained in the original submission for Technology Appraisal 600,[8] with multiple imputation by chained equations (MICE) used to handle missing data. The hazard ratio (HR) for PFS estimated from the MAIC was 0.28 (95% confidence interval [CI] 0.16 to 0.49 with an effective sample size (ESS) of 84 patients. This is slightly higher (less favourable) than the HR obtained from the company's original ITC (HR = 0.25, 95% CI 0.11, 0.57). The company's TE response includes a scenario analysis using this HR in the economic model which increases the company's updated base case ICER from [redacted] to [redacted] per QALY gained.

Issue 2: The company's model predictions of health state occupancy are not plausible

The company's TE response[1] does not contain any additional evidence or analysis regarding the plausibility of the model predictions. However, the company suggests that the ERG's concerns are resolved to some degree within the ERG's preferred analysis. The company states that they would be interested in the views of other professional groups, specifically the Royal College Pathologists (RCP) and the British Society for Haematology (BSH), regarding the plausibility of the model predictions.

3. ERG critique of the company's TE response

Issue 1: The evidence used to inform the company's CDF model remains highly uncertain

The ERG's concerns regarding the company's original approach to modelling PFS can be found in Section 4.2.4 of the ERG report.[9] The company's updated base case following TE is the same as the ERG's preferred analysis. This analysis re-estimates PFS for the ibrutinib group by assuming a proportional relationship between TTD and PFS in the Rory Morrison Registry (RMR) dataset, and then applying this HR to the parametric survival model for TTD from SACT[5] as a baseline (see ERG report Section 4.3).

The ERG agrees that the company's scenario analysis using TTNT data from SACT[5] as a proxy for PFS likely provides an upper bound for PFS. The ERG notes that the company's economic model assumes that [redacted] of patients do not receive active subsequent-line treatment and instead receive BSC alone. This does not appear to have been explicitly accounted for in the time-to-event analysis, as only receipt of a new regimen and death were counted as events. This may mean that TTNT in SACT is overestimated. Nonetheless, the ERG believes that this scenario analysis is useful in providing an estimate of the lower bound for the ICER, subject to the other assumptions in the model. The ERG agrees with the company that the ERG's preferred analysis provides a more reasonable base case scenario and that the true PFS will probably lie somewhere between TTD and TTNT.

The ERG believes that the company's additional MAIC is useful in providing supporting evidence of the relative treatment effect on PFS for ibrutinib versus Physicians' Choice (PC). The ERG notes two main concerns regarding this analysis. Firstly, the absence of evidence indicating a violation of the proportional hazards (PH) assumption does not guarantee that the PH assumption holds, and the reduced sample size may contribute to the finding of a non-statistically significant *p*-value. The log cumulative hazards plots presented in Figure 5 of the company's TE response appendix[2] also suggest that there are some violations of the PH assumption. Secondly, statistical testing for PH does not consider the unobserved period for which data do not exist. Therefore, performing survival extrapolation without reliance on the PH assumption would be preferred. This approach was suggested in the ERG report[9] (Section 4.2.4); however, the company's TE response[1] explains that this type of analysis has not been explored due to time limitations.

The ERG notes that owing to the uncertainties in the evidence used to inform the ITC, it is important to consider whether the application of the relative treatment effect estimate (the HR for PFS) within the economic model produces plausible predictions of PFS and overall survival (OS) for patients receiving PC.

Issue 2: The company's model predictions of health state occupancy are not plausible

The ERG report[9] highlighted concerns regarding several predictions of the company's CDF model which were not deemed plausible by the ERG's clinical advisor:

(a) Ibrutinib group: The model suggests a large gap between TTD and PFS (mean lag of 1.18 years).
(b) Ibrutinib group: The model suggests only a small gap between PFS and OS in the ibrutinib group (0.41 years).
(c) PC group: The model predicts that virtually all PC-treated patients will have died after around 6 years after starting treatment for relapsed/refractory (RR) Waldenström's macroglobulinaemia (WM).

As described in Section 2 of this addendum, the company's TE response does not present any further evidence or analyses to inform the plausibility of the overall model predictions. However, additional relevant information is contained within the TE submissions from the two clinical experts.[3, 4] In addition, the ERG sought further information from their clinical advisor regarding expected PFS and OS for the ibrutinib group and expected OS for the PC group. The views of the three advisors are summarised in

Table 1.

Table 1: Summary of clinical advisors' views

Model prediction	Advisor 1 (ERG)	Advisor 2 (NICE)	Advisor 3 (NICE)
(a) Ibrutinib group: Gap between TTD and PFS	Patients usually stay on treatment until the point of progression, and those who discontinue before that point progress soon after treatment is stopped.	Agrees with Advisor 1	5-10% of patients will stop ibrutinib before progressing due to intolerance. Patients would not have a lag between stopping ibrutinib and progressing as they would progress whilst on ibrutinib and there would be a period of time when potentially they remain on ibrutinib because of ongoing clinical benefit and no indication for next line of therapy but technically in the progressed state.
(b) Ibrutinib group: Gap between PFS and OS	At least two thirds of progressed patients would respond to salvage therapy after ibrutinib for a few years (3-4 years), and it is *"definitely not half a year."* The advisor shared a publication (Gustine *et al*, 2018[10]) which reports a response rate of 71% and a median OS of 21-32 months after ibrutinib discontinuation.	Agrees with Advisor 1 that the gap is not considered to be plausible and that patients who progress on ibrutinib are sometimes salvageable on 3L and 4L chemotherapy.	The advisor stated that they expect the median time between PFS and OS to be *"a lot longer"*. As can be seen from the RMR and published real world data, patients can still achieve good responses with repeated lines of chemoimmunotherapy, although the duration of response may be shorter compared to first-line.
(c) PC group: Expected OS at 6 years	At 6 years, the proportion of surviving patients on PC would be half of that for patients on ibrutinib.	Agree with Advisor 1 that the company's prediction that virtually all PC-treated patients die by 6 years after starting initial treatment for RR WM is unrealistic as some patients survive beyond 6 years.	More people will be alive at this time point as demonstrated by the ECR.[7]

3L - third line; 4L - fourth line; ECR - European Chart Review; PC - physicians' choice; PFS - progression-free survival; OS - overall survival; RMR - Rory Morrison Registry; TTD - time to treatment discontinuation; RR – relapsed/refractory; WM - Waldenström's macroglobulinaemia

4. Additional analyses undertaken by the ERG

The ERG has undertaken an additional scenario analysis which reflects their clinical advisor's view regarding expected OS for the PC group. The clinical advisor suggested that at 6 years, the probability that a patient initiating PC treatment for RR WM would be half of that for patients receiving ibrutinib. The company's model predicts a 6-year OS probability for patients on ibrutinib of 25%. The ERG notes that the key parameter which drives OS for patients on PC is the HR from the ITC. Hence, the ERG calculated the HR required in order for the model to predict a 6-year OS probability for PC of 12.5%. This HR was estimated to be 0.74 (see Figure 1).

Figure 1: Model-predicted OS in company's updated base case and ERG additional scenario analysis

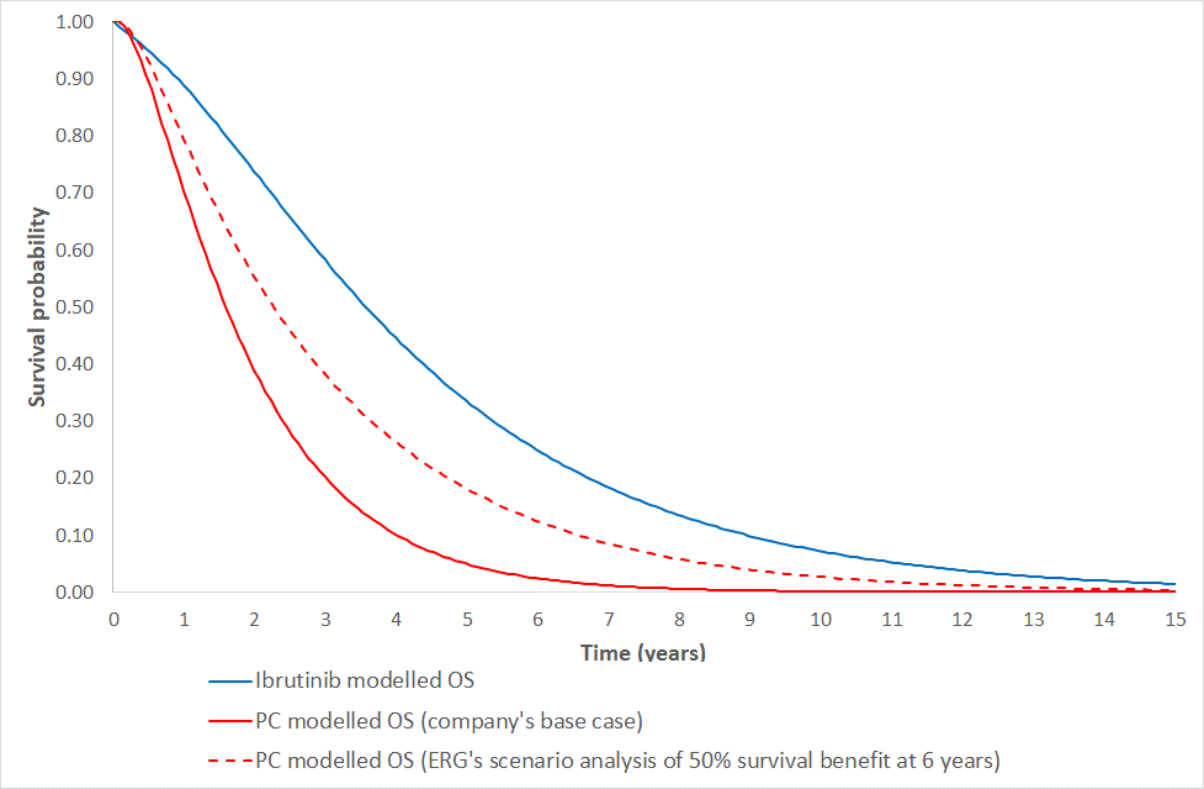

Table 2 presents the results of the ERG's additional scenario analysis. As shown in the table, applying an HR for PFS of 0.74 increases the ERG's preferred ICER from [redacted] to [redacted] per QALY gained. The ICER for this scenario is increased largely as a consequence of greater OS and QALY gains for the PC group due to the less favourable inverse HR applied to the ibrutinib PFS model. The ERG notes that whilst this analysis reflects the ERG's clinical advisor's expectation of 6-year OS for the PC group, the structural limitations of the model, including the reliance on the PH assumption, does not guarantee that the overall survival distribution applied in the scenario is plausible (i.e. the analysis involved amending a single model parameter [the HR for PFS] to force the modelled OS projection to run through a single data-point).

Table 2: Additional scenario analysis undertaken by the ERG - 6-year OS for PC equals 50% of 6-year OS for ibrutinib

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
ERG-preferred analysis							
Ibrutinib	4.86	[redacted]	[redacted]	2.88	[redacted]	[redacted]	[redacted]
PC	1.98	[redacted]	[redacted]	-	-	-	-
Additional scenario analysis assuming 6-year OS for PC equals 50% of 6-year OS for ibrutinib							
Ibrutinib	4.86	[redacted]	[redacted]	1.81	[redacted]	[redacted]	[redacted]
PC	3.05	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group; PC - physician's choice; OS - overall survival
** Undiscounted*

5. References

1. Janssen-Cilag. Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]. Company's technical engagement response. High Wycombe, UK; 2021.
2. Janssen-Cilag. Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]. Company's technical engagement response - appendices. High Wycombe, UK; 2021.
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4. El-Sharkawi D. Ibrutinib for treating Waldenstrom's macroglobulinaemia (CDF Review of TA491) [ID3778] - clinical expert statement and technical engagement response 2021:1-15.
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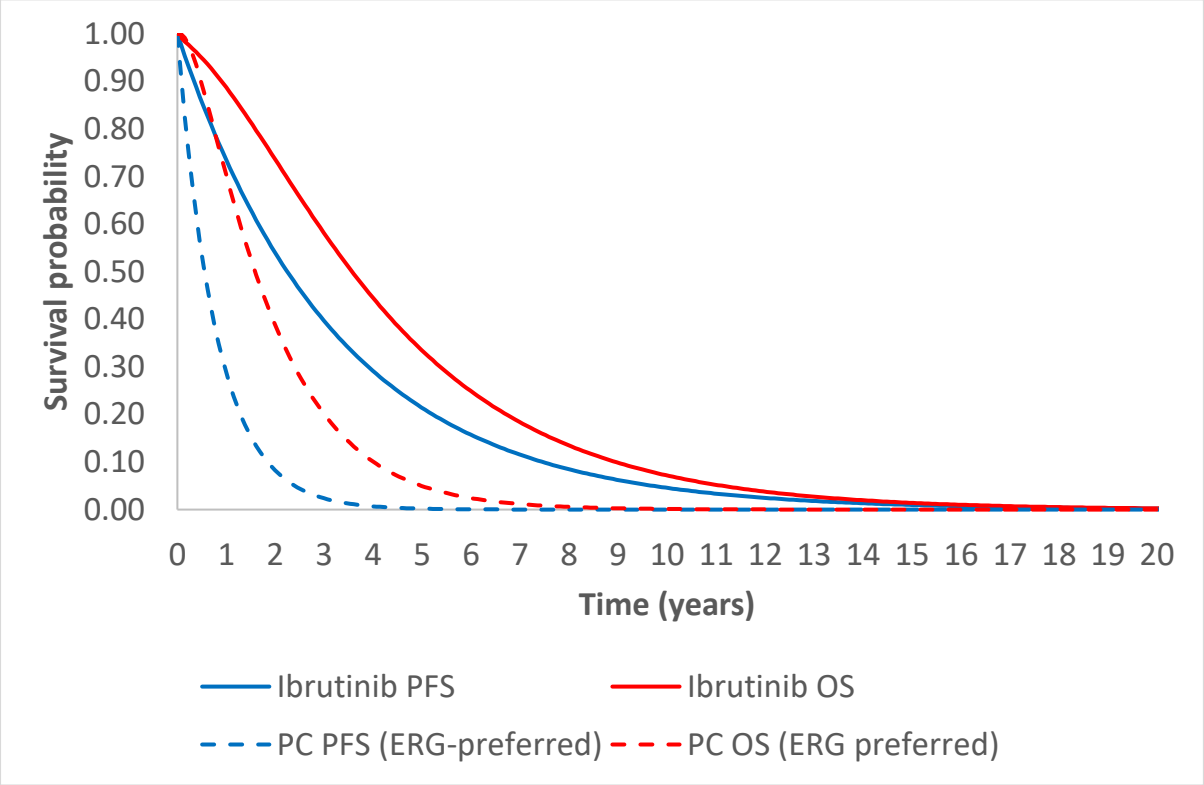
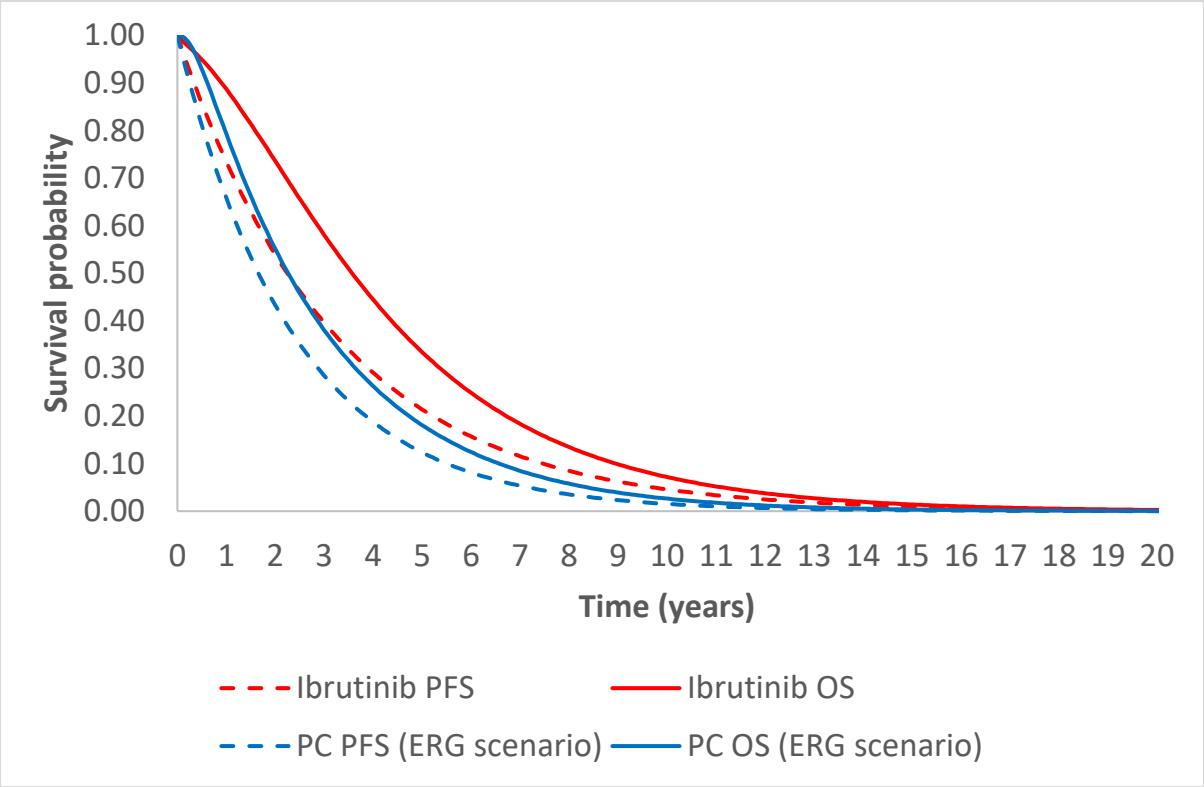
6. Treon SP, Meid K, Gustine J, Yang G, Xu L, Liu X*, et al.* Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenstrom Macroglobulinemia. *Journal of Clinical Oncology* 2020;39:565-75.
7. Buske C, Sadullah S, Kastritis E, Tedeschi A, García-Sanz R, Bolkun L*, et al.* Treatment and outcome patterns in European patients with Waldenström's macroglobulinaemia: A large, observational, retrospective chart review. *The Lancet Haematology* 2018;5:e299-e309.
8. Janssen-Cilag. Single Technology Appraisal: Ibrutinib for treating Waldenström's macroglobulinaemia [ID884] - Company's evidence submission. High Wycombe, UK; 2016.
9. Metry A, Tappenden P, Pandor A, Orr M. Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]. Sheffield, UK; 2021.
10. Gustine JN, Meid K, Dubeau T, Severns P, Hunter ZR, Guang Y*, et al.* Ibrutinib discontinuation in Waldenström macroglobulinemia: Etiologies, outcomes, and IgM rebound. *American Journal of Hematology* 2018;93:511-7.

Company base-case/ERG preferred model predicted survival outcomes for ibrutinib and PC



ERG scenario analysis (PC survival 50% of ibrutinib survival at 6 years)



Mean time in state – ERG preferred model / company's updated base case

Endpoint	Mean time	
	Ibrutinib	PC
TTD	3.24	0.80
PFS	3.71	0.80
PPS	1.16	1.18
OS	4.86	1.98