Confidential until published

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

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
	Abdullah Pandor, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Martin Orr, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	26th August 2021 (post-factual accuracy check)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 13/18/43.

Declared competing interests of the authors

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

Acknowledgements

We would like to thank Dr Jaimal Kothari for clinical advice relating to this project. We would also like to thank Dr Aline Navega Biz, ScHARR, for providing comments on the draft report, and Gill Rooney, ScHARR, for providing administrative support and in preparing and formatting the report.

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.

This report should be referenced as follows:

Metry A, Tappenden P, Pandor A, Orr M. Ibrutinib for treating Waldenström's macroglobulinaemia (CDF Review of TA491) [ID3778]. School of Health and Related Research, University of Sheffield, 2021.

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.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

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

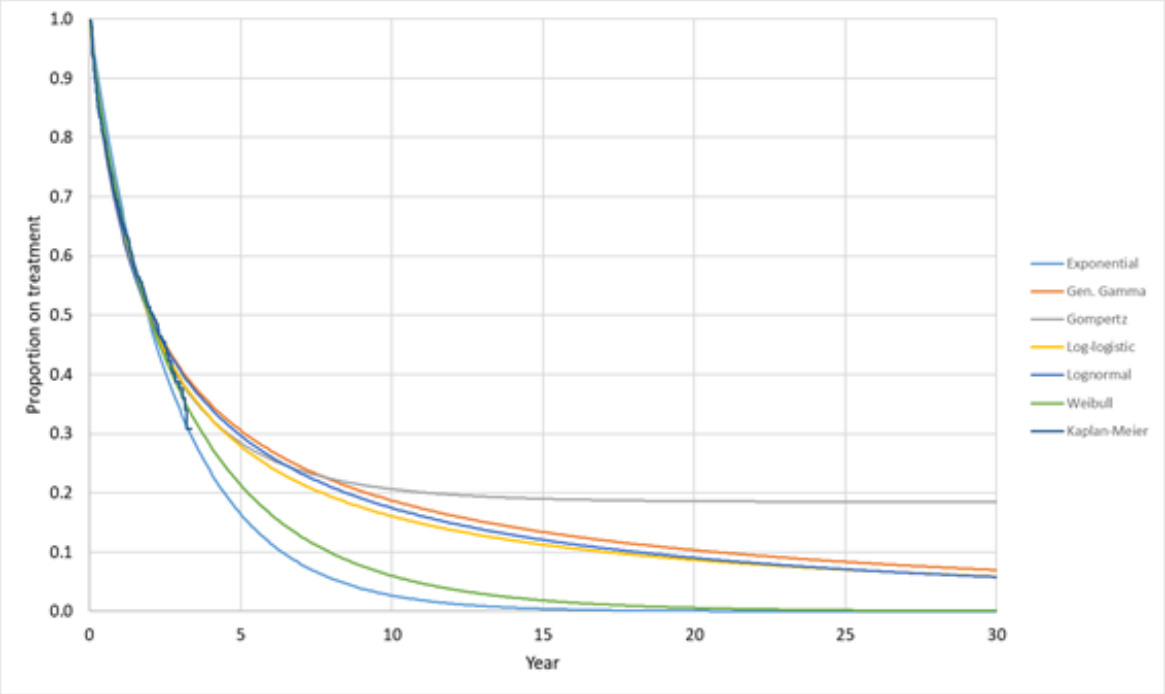
The TA491 model[1] assumed that TTD for ibrutinib was equivalent to PFS (i.e. patients are treated until disease progression); hence, TTD was not modelled separately to PFS. In contrast, the CDF model assumes that TTD and PFS are not equivalent. The CDF-CS[7] notes that *"over the course of the data 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)

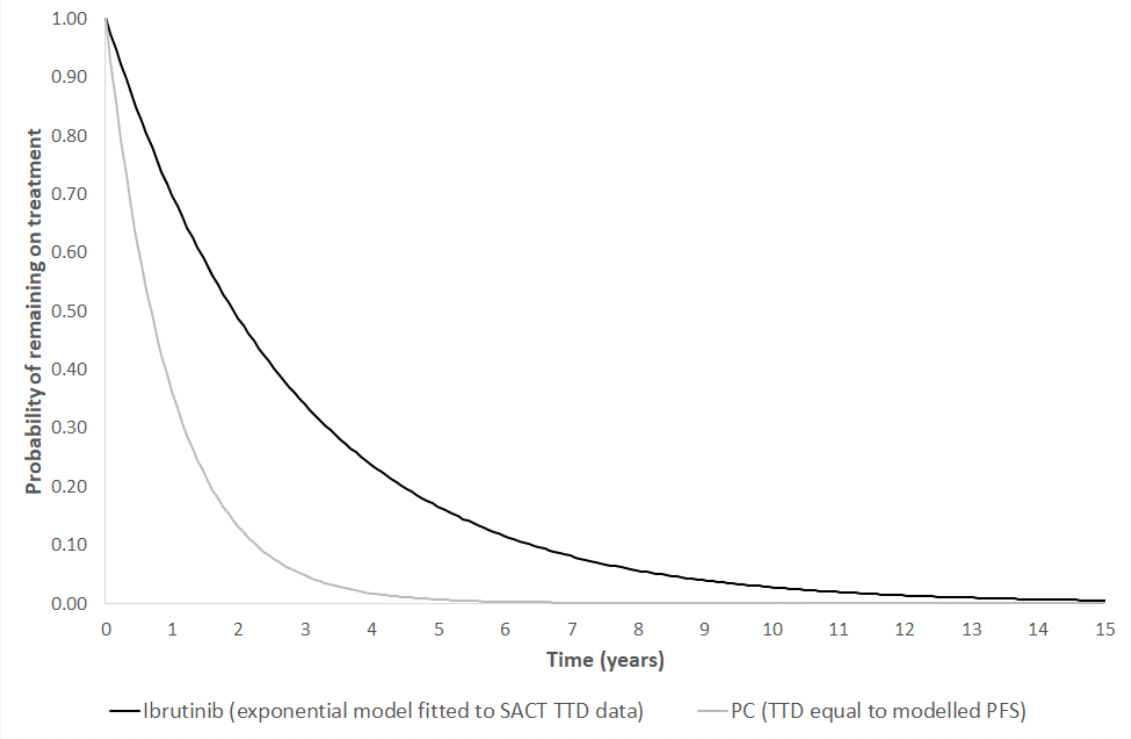
Model	AIC	BIC
Exponential	3325.43	3330.14
Weibull	3315.91	3325.34
Gompertz	3314.04	3323.46
Log-normal	3298.48	**3307.90**
Log-logistic	3311.00	3320.43
Generalised gamma	**3300.28**	3314.41

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

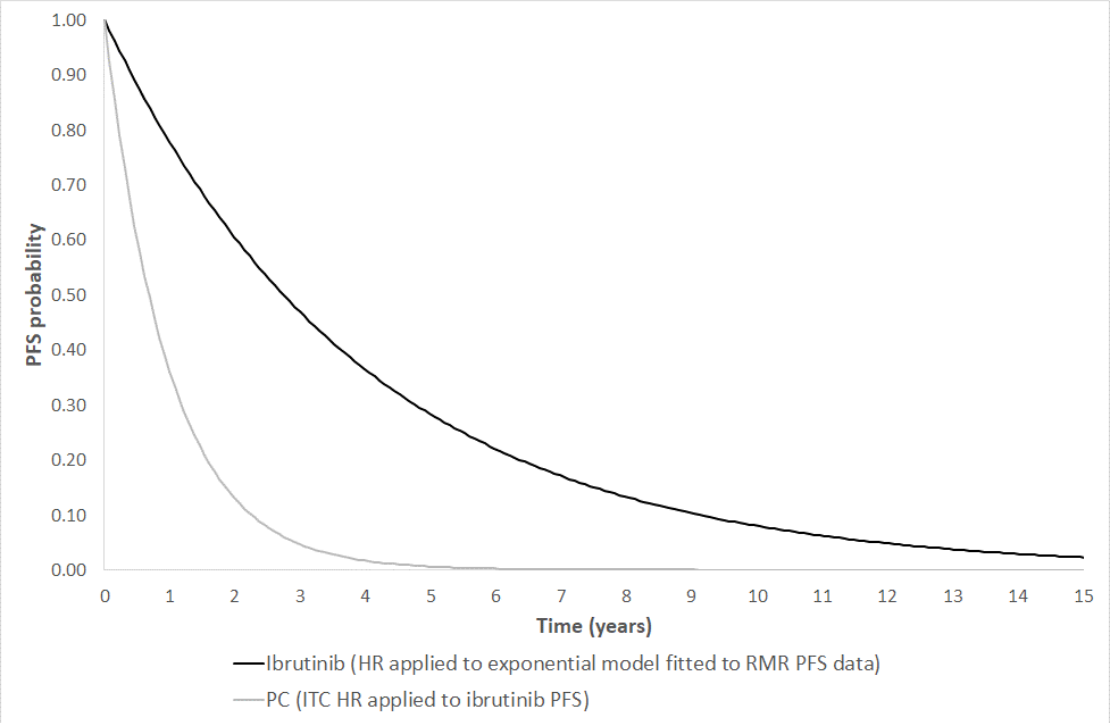
Bold indicates best-fitting model
AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

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]

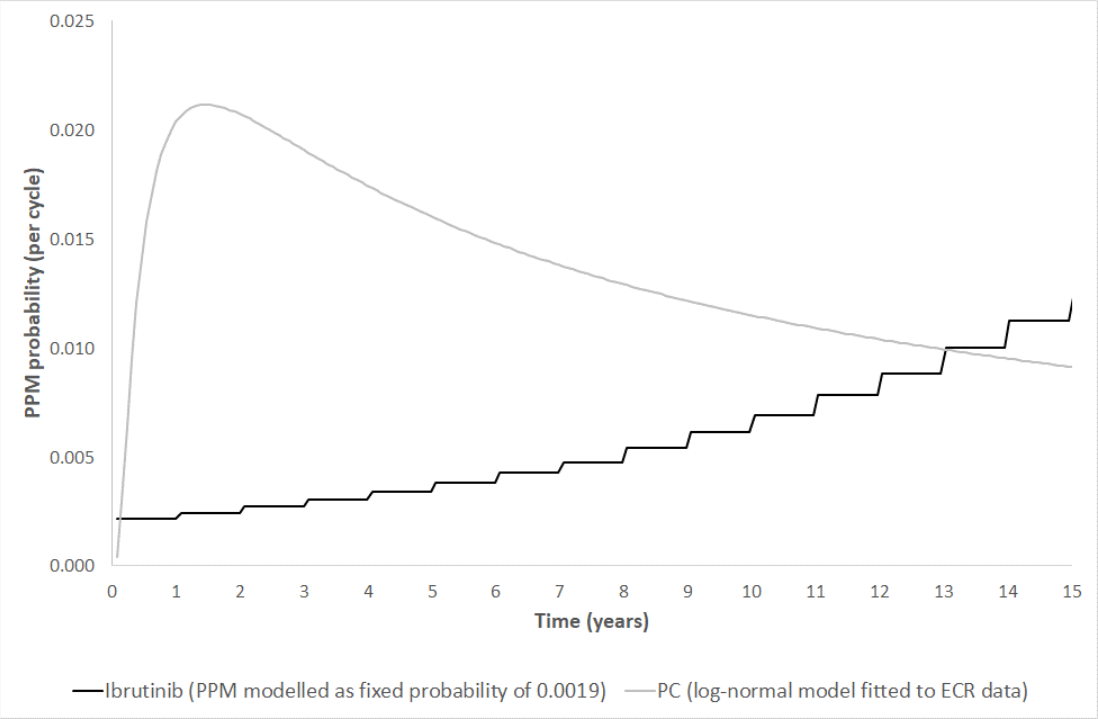
The company's CDF base case model retains the PPM probability applied in the ERG's exploratory analyses in TA491.[5] This PPM estimate was based on the earlier 24-month data-cut of Study 1118E, and was based on 3 death events (PPM probability per 28-day model cycle = 0.0019).[2]

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)

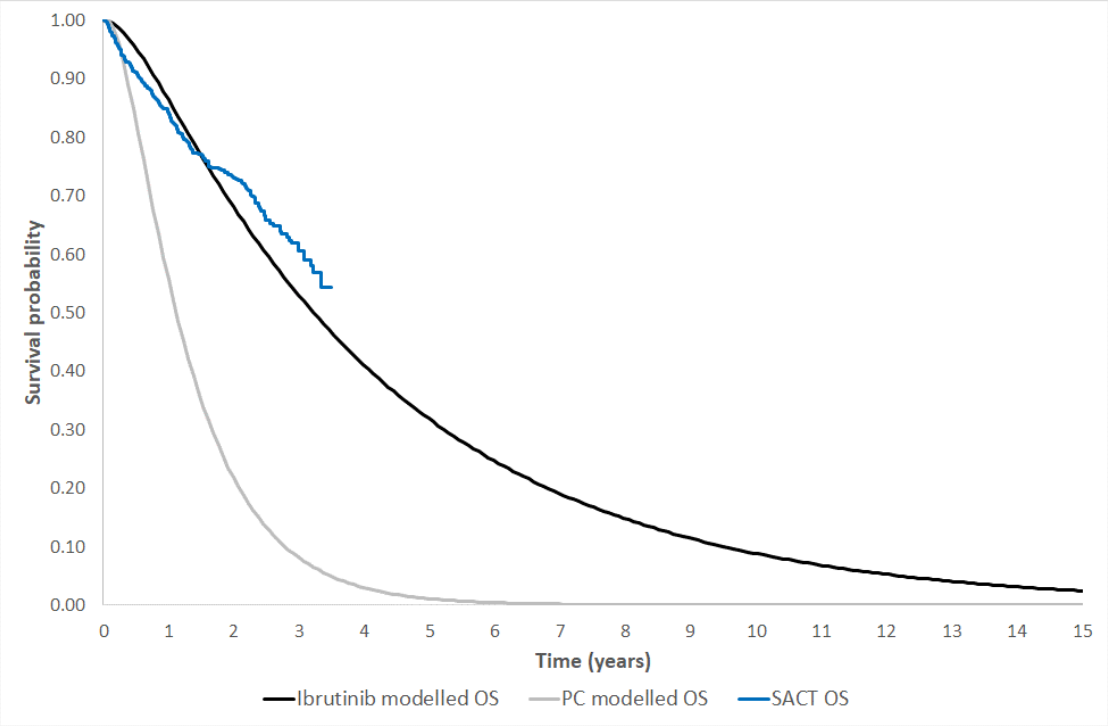


ECR - European chart review; PC - physician's choice; PPM - pre-progression mortality

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.

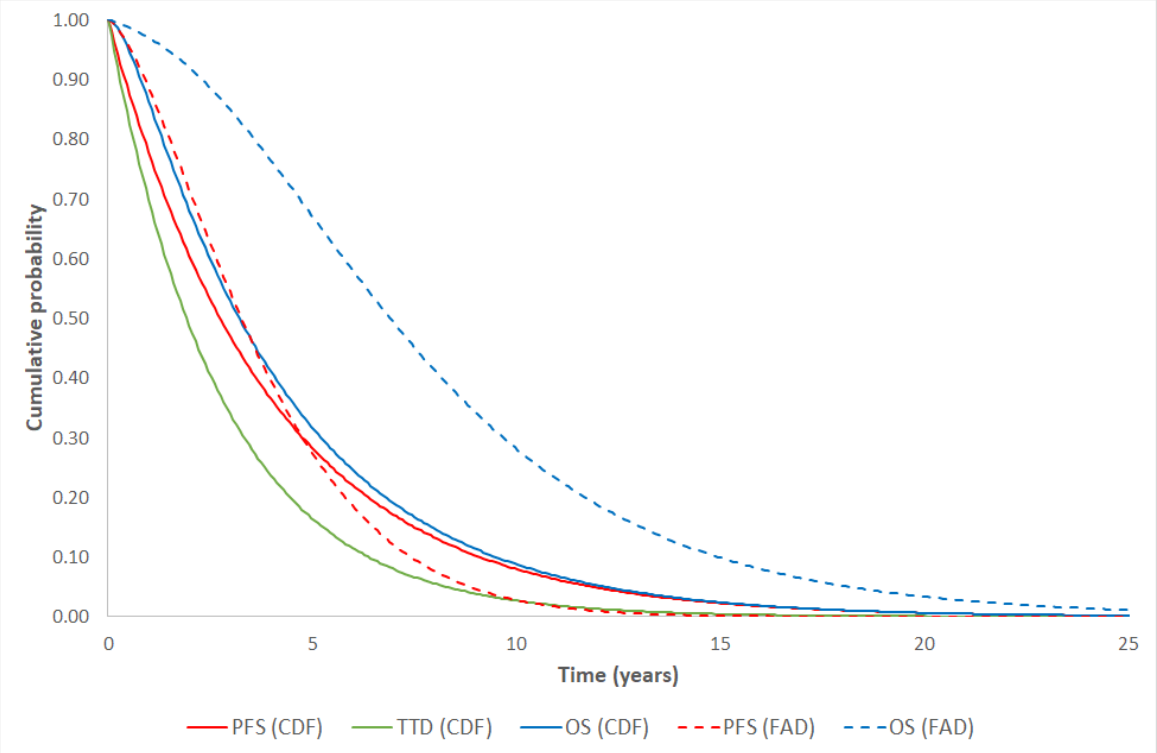
The third issue relates to the extent to which the CDF model adheres to the ToE for the CDF guidance review. The ToE document (Table 3) states that the company *"should use more mature, PFS and OS data using data collected through SACT, Study 1118E, iNNOVATE and the WMUK (RMR) Registry."*[6] The ERG 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

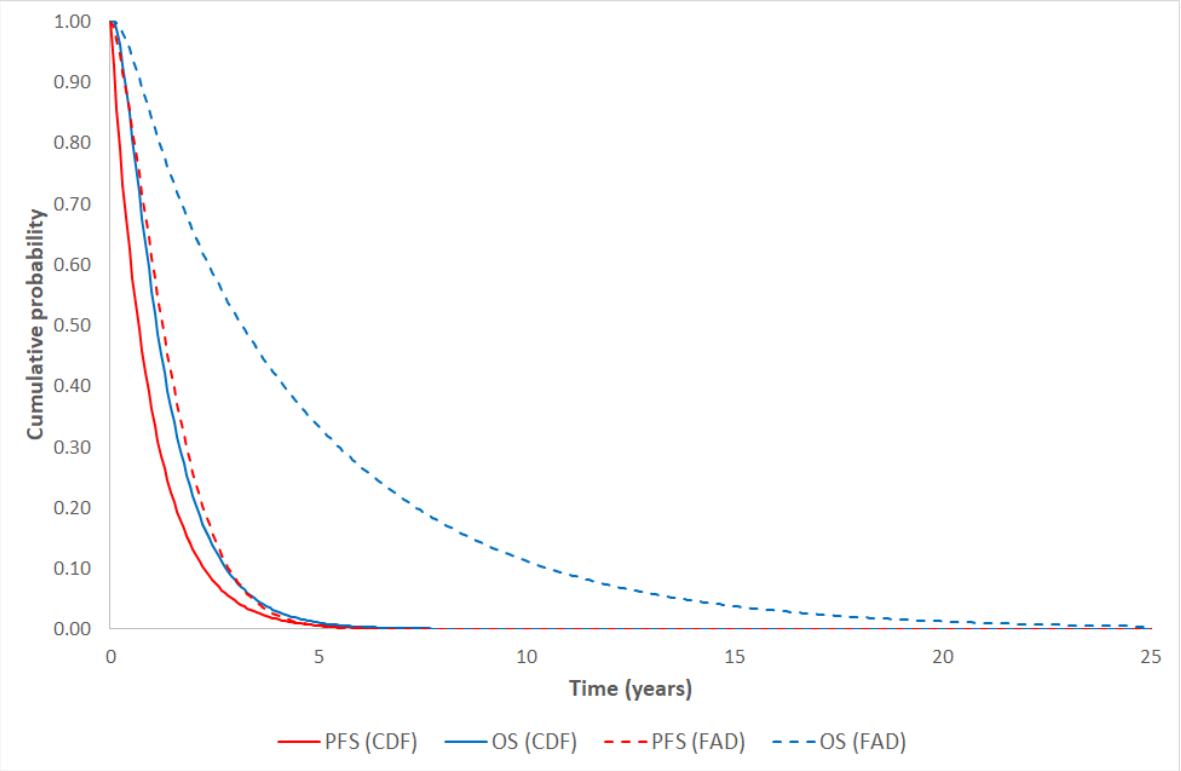
The ERG has concerns regarding the plausibility of the company's CDF model predictions and notes that these differ considerably from the predictions of the original TA491 model. Figure 11 and Figure 12 present comparisons of model-predicted TTD, PFS and OS from the original TA491 model (dashed lines) 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.

7. REFERENCES

1. Janssen-Cilag. Single Technology Appraisal: Ibrutinib for treating Waldenström's macroglobulinaemia [ID884] - Company's evidence submission. High Wycombe, UK; 2016.
2. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R*, et al.* Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *New England Journal of Medicine* 2015;372:1430-40.
3. National Institute for Health and Care Excellence. Final Appraisal Determination - Ibrutinib for treating Waldenstrom's macroglobulineamia. London, UK; 2017.
4. 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.
5. Tappenden P, Carroll C, Stevens J, Simpson E, Thokala P, Sanderson J*, et al.* Ibrutinib for treating Waldenström's macroglobulinaemia – Evidence Review Group report. Sheffield, UK; 2016.
6. National Institute for Health and Care Excellence. Terms of engagement for CDF review - Ibrutinib for treating Waldenstrom's macroglobulinaemia (TA491). London, UK; 2021.
7. Janssen-Cilag. CDF review: Ibrutinib for treating Waldenström's macroglobulinaemia [ID3778]. Company's evidence submission. Wycombe, UK; 2021.
8. Dimopoulos MA, Trotman J, Tedeschi A, Matous JV, Macdonald D, Tam C*, et al.* Ibrutinib Therapy in Rituximab-Refractory Patients with Waldenström's Macroglobulinemia: Initial Results from an International, Multicenter, Open-Label Phase 3 Substudy (iNNOVATETM). *Blood* 2015;126:2745-.
9. Janssen-Cilag. CDF review: Ibrutinib for treating Waldenström's macroglobulinaemia [ID3778]. Company evidence submission - appendices. High Wycombe, UK; 2021.
10. Public Health England. Ibrutinib for treating Waldenström's macroglobulinaemia: data review - Systemic anti-cancer therapy (SACT) Final Report; 2021.
11. Janssen-Cilag. Rory Morrison Registry (RMR) dataset [data held on file]. High Wycombe, UK; 2021.
12. Jørgensen J, Kefalas P, . Upgrading the SACT dataset and EBMT registry to enable outcomes-based reimbursement in oncology in England: a gap analysis and top-level cost estimate. *Journal of Market Access and Health Policy* 2019;7.
13. Janssen-Cilag. CDF review - Ibrutinib for treating Waldenström's macroglobulinaemia [ID3778]. Company's response to clarification questions from the ERG. High Wycombe, UK; 2021.
14. 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.
15. Pharmacyclics Inc. Clinical Study Report: iNNOVATE Study, A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenstrom's Macroglobulinemia - Final Analysis Arm C; 2020.
16. Bomsztyk J, D'Sa S, McCarthy H, Scorer H, El-Sharkawi D, Pratt G*, et al.* First UK Waldenström's Macroglobulinaemia Registy report. Henley-on-Thames, UK: WMUK; 2018.
17. Bomsztyk J, D'Sa S, McCarthy H, El-Sharkawi D, Scorer H, Kothari J*, et al.* PF621. Real world experience in the management of Waldenström's Macroglobulinaemia from analysis of the Rory Morrison Registry. Paper presented at: European Hematology AssociationJune 14, 2019.
18. Office for National Statistics. National life tables. London, UK 2015.
19. Tedeschi A, Benevolo G, Varettoni M, Battista ML, Zinzani PL, Visco C*, et al.* Fludarabine plus cyclophosphamide and rituximab in Waldenström macroglobulinemia: an effective but

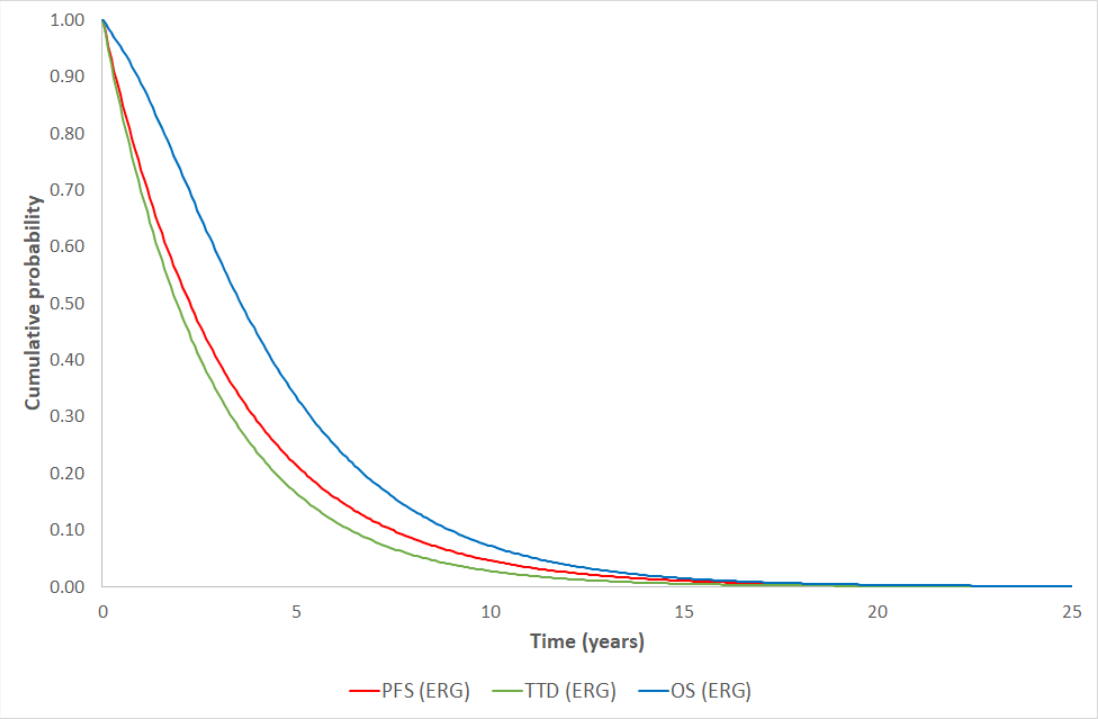
myelosuppressive regimen to be offered to patients with advanced disease. *Cancer* 2021;118:434-43.

20. Tedeschi A, Ricci F, Goldaniga MC, Benevolo G, Varettoni M, Motta M*, et al.* Fludarabine, cyclophosphamide, and rituximab in salvage therapy of Waldenström's macroglobulinemia. *Clinical Lymphoma, Myeloma and Leukemia* 2013;13:231-4.
21. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Zervas K, Tsatalas C, Kokkinis G*, et al.* Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *Journal of Clinical Oncology* 2007;25:3344-9.
22. Treon SP, Branagan AR, Ioakimidis L, Soumerai JD, Patterson CJ, Turnbull B*, et al.* Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia. *Blood* 2009;113:3673-8.
23. Electronic Medicines Compendium. MabThera 100mg and 500mg concentrate for solution for infusion; 2016 (available from: http://www.medicines.org.uk/emc/medicine/20590).
24. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM*, et al.* Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *New England Journal of Medicine* 2014;371:213-23.
25. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A*, et al.* Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health and Quality of Life Outcomes* 2010;8.
26. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *European Journal of Health Economics* 2013;14:749-59.
27. European Medicines Agency. Summary of Product Characteristics (SmPC): Imbruvica. London, UK; 2021.
28. Pharmacyclics Inc. Clinical Study Report: Phase 2 study of Bruton's tyrosine kinase inhibitor (BTK), ibrutinib (PCI-32765), in Waldenstrom's Macroglobulinemia. PCYC-1118E. California, UK; 2014.
29. BMJ Group, Britain RPLatRPSoG. British National Formulary (online). . London; 2016.
30. MIMS. Monthly Index of Medincines Specialty (Online); 2020.
31. eMIT. Drugs and pharmaceutical electronic market information tool (eMIT). NHS Commercial Medicines Unit (CMU); 2020. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (Accessed 23 September 2020).
32. NHS England. NHS Reference Costs (2014-2015). London, UK; 2015.
33. NHS England. NHS Reference Costs (2018-2019). London; 2019.
34. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. *Palliative medicine* 2015;29:899-907.
35. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC medical research methodology* 2012;12:9.
36. Office for National Statistics. National Life Tables (2017-2019). London, UK; 2020.
37. Phillippo DM, Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from http://www.nicedsu.org.uk.

8. APPENDICES

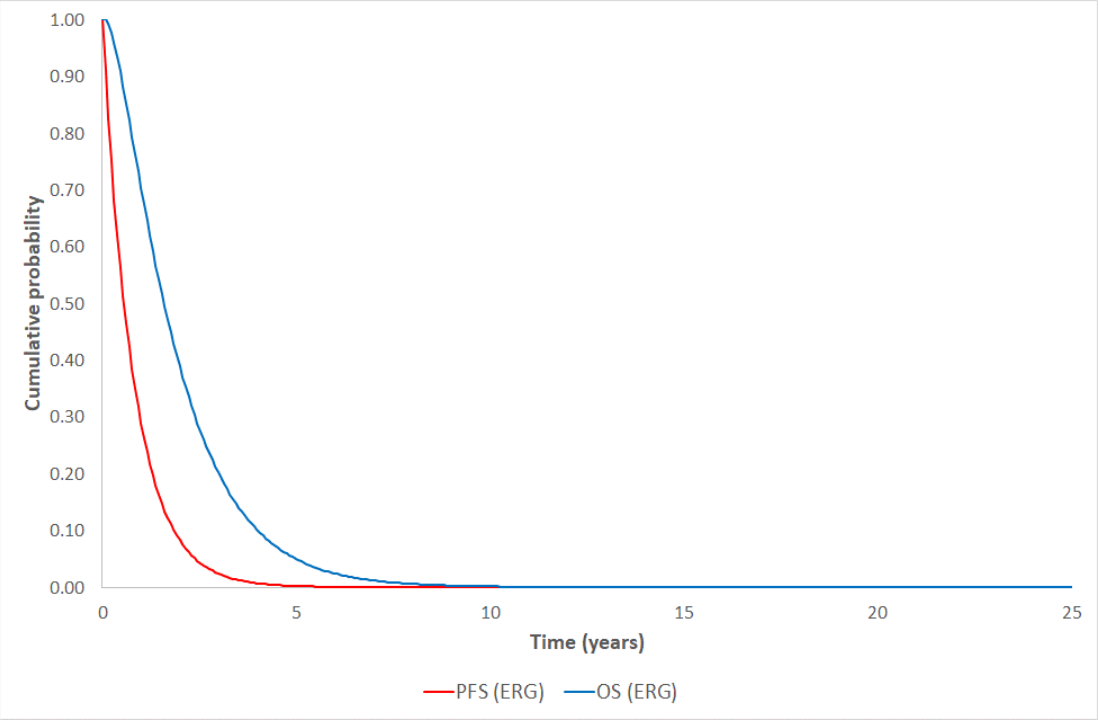
Appendix 1: Model-predicted TTD, PFS and OS from ERG's preferred analysis

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