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Ibrutinib for treating Waldenström's macroglobulinaemia CDF review TA491

Lead team presentation

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7th December 2021

Key clinical issues

1) The company previously used data from Study 1118E in its base-case for ibrutinib efficacy, but the revised base case uses Systemic Anti-Cancer Therapy (SACT) data from its use in the Cancer Drugs Fund. Are data from SACT the most appropriate and generalisable evidence for people who would have ibrutinib in NHS clinical practice?

    - Would ibrutinib be used earlier in the treatment pathway in the future i.e. after only 1 prior therapy and does this affect the generalisability of the SACT data to future NHS clinical practice?

2) The company's hazard ratio for progression free survival for ibrutinib vs standard care as used in TA491 was XXXX, based on a comparison of the progression free survival from study 1118E compared with matched patients from an observational European chart study. Is this figure clinically plausible, and transferable to this Cancer Drugs Fund review?

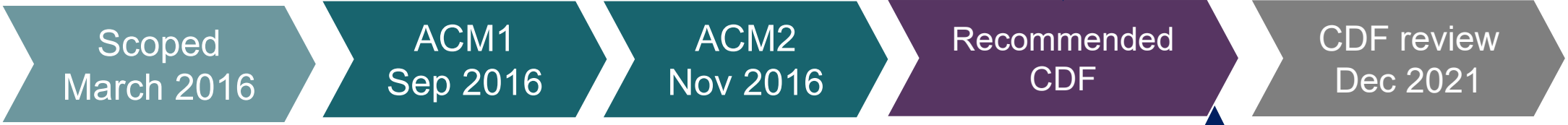
Ibrutinib (Imbruvica, Janssen)

Marketing authorisation July 2015	Monotherapy for treating adults with Waldenström's macroglobulinaemia: • who have had at least 1 prior therapy, or • as first-line treatment in patients for whom chemo-immunotherapy is unsuitable.
Mechanism of action	Selective inhibitor of Bruton's tyrosine kinase (BTK), stopping B-cell (lymphocyte) proliferation and promoting cell death
Administration and dose	420 mg orally once daily until disease progression or there is unacceptable toxicity.
List price	List price: £4,599.00 for 1 pack of 90×140 mg capsules (£51.10 per capsule) Cost per year of treatment : £55,954.50 (median treatment duration with ibrutinib is 24.9 months per the Systemic Anti-Cancer Therapy (SACT) 3-year data) Confidential patient access scheme approved (simple discount)

Summary of original appraisal TA491

Optimised Cancer Drugs Fund (CDF) recommendation

Ibrutinib is recommended for use in the CDF as an option for treating Waldenström's macroglobulinaemia in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed **(CDF recommendation did not include people for whom chemoimmunotherapy is unsuitable, a population included in the marketing authorisation)**



1) Managed access agreement
2) Additional data from:
- SACT (Systemic Anti-Cancer Therapy dataset)
- Phase 2 registration study 1118E
- Phase 3 study 1127 [iNNOVATE, arm C only]

Waldenström's macroglobulinaemia (WM): disease background

- Specific, relatively rare type of non-Hodgkin's lymphoma. Lymphomas are cancers of the lymphatic system caused by abnormal B cells which produce immunoglobulin M (IgM). IgM can thicken the blood, reducing flow through capillaries which can cause nerve damage in the hands and feet
- Effects on the bone marrow can cause anaemia, neutropenia and thrombocytopenia
- Symptoms include severe fatigue, night sweats, lack of concentration, frequent/persistent infections, breathlessness, sinus problems and weight loss
- WM develops slowly, most people have no symptoms in the early stages of the disease and are diagnosed in advanced stages
- Rare, approximately 330 people are diagnosed with WM in England annually; data collected in the Cancer Drugs Fund showed 823 people had treatment with ibrutinib
- More common in men; mainly affects people 70 years and older
- WM has a long disease trajectory; median overall survival ranges from less than 4 years to 12 years. Nearly half of people diagnosed die from causes unrelated to WM

Current management

- No established standard of care for treating WM; no published NICE guidance relating to diagnosis or treatment of WM
- Asymptomatic:
  - observation until disease becomes symptomatic
- Symptomatic:
  - Number of treatment options (generally rituximab based) suggested in guidelines by:
    - British Committee for Standards in Haematology
    - European Society for Medical Oncology
- Prior to the introduction of BTK inhibitors such as ibrutinib, common options included a range of single and combination therapies that were developed for other lymphoproliferative diseases
- Chemotherapy options dependent on the performance status, clinical features and comorbidities

Comparators for ibrutinib /current chemotherapy options for people who have received at least 1 prior therapy

- Rituximab and bendamustine
- Rituximab, dexamethasone and cyclophosphamide
- Rituximab and fludarabine with or without cyclophosphamide
- Cladribine with or without rituximab
- Rituximab
- Chlorambucil

Source: NICE scope for CDF review

Patient organisation perspective

Impact of WM

- Fear around lack of treatment and risk of relapse affects mental wellbeing
- Treatment aimed at minimising burden of disease not cure
- Symptoms like fatigue can be intense, disabling and have significant impact on day-to -day life
- “Watch and wait” stressful for patients, family and carers

People would like

- Well-tolerated treatment, targeted therapy that provides long-term disease control
- Improved quality and length of life
- Treatment options whilst waiting for recurrence
- Median age at diagnosis is 70. Patients vulnerable to multiple complications and have mobility issues . Oral therapy particularly valuable for this population

Ibrutinib

- Step-change in managing WM; life transforming and fast-acting
- Effective, durable disease control with improved survival and ability to induce remission
- Well tolerated
- Improved quality of life compared to chemotherapy
- Oral treatment that can be taken at home, saving outpatients appointments

Clinical expert perspective

- WM typically follows a relapsing and remitting course over many years; patients will receive many different forms of chemotherapy
- Ibrutinib is an effective non-chemoimmunotherapy option for patients with relapsed or refractory WM
- Morbidity and mortality associated with WM not due to disease itself but other causes indirectly related to it
- WM affects primarily older age group, who are vulnerable to multiple complications, ibrutinib offers an important addition to treatment options
- Offers a treatment option when chemotherapy or further lines of chemotherapy are not suitable
- Number of patients offered ibrutinib via CDF much higher than expected and reflects unmet need:
    - All patients who had 1 or more treatments may have been offered ibrutinib~ number may decrease as likely ibrutinib will predominantly be offered as a second or third line, rather than as a later line treatment in the future
- Period of remission lasts between 2 and 6 years (median 4-5 years)
- Even after disease progression, patients may stay on treatment as there may be no indication to change treatment immediately

Clinical evidence presented in TA491

Intervention	Data source	Results	Committee comments
Ibrutinib	**Study 1118E** (open-label, single arm study without a control group). **Population**: adults with WM who had at least 1 previous therapy (**n=63**)	**24 months follow up:** • **Overall response rate (ORR)** 90.5% (95% confidence interval [CI] 80.4 to 96.4) **37 months follow up:** • **Progression free survival (PFS)**: 82.0% (95% CI, 69.1 to 89.9) • **Overall survival (OS)**: 90.0% (95% CI, 77.4 to 95.8)	**Study 1118E** Reasonable quality, generalisable to clinical practice but limited by lack of comparison against a treatment used in the UK **ARM C iNNOVATE** Early data, longer follow up data could resolve some clinical uncertainties **All studies** Lack of trial data for people whom chemo-immunotherapy is unsuitable a limitation of evidence base
	Arm C iNNOVATE trial (open-label sub-study of 1 arm of trial, with no comparator) **Population**: people who relapsed within 12 months of rituximab-containing treatment (**n=31**) Note: this population could have poorer prognosis	**17 months follow up** **ORR** 90% **PFS** at 1 year 93%	

- **In the absence of comparator data for other treatments, what do these results indicate about the effectiveness of ibrutinib?**

Clinical evidence presented in TA491

Intervention	Data source	Results	Committee comments
Comparator: standard therapies "Physicians choice" (**PC**) blend of alternative second line rituximab/ chemotherapy options	Retrospective, observational study based on chart review of people with WM: European Chart Review (**ECR**) **Population:** data from patient records for treatment-naïve and patients with relapsed WM across 10 European countries gathered by survey from December 2014 to January 2015 (n=454; 72 from UK) Up to 4 lines of treatment cohort (n=175) "matched" with subset of patients from study 1118E (n=47) used in indirect comparison	**Indirect treatment comparison (ITC):** ITC estimated the hazard ratio for PFS for ibrutinib (using data from study 1118E) versus standard therapies. Multivariable Cox proportional hazards model produced an estimated hazard ratio (HR) for PFS for ibrutinib versus standard therapies of [redacted] (95% CI: [redacted]) 4 different approaches taken by company to estimating comparative effectiveness showed PFS benefit for ibrutinib vs. comparator → Hazard ratio (HR) [redacted] to [redacted]	Noted ERG's concerns regarding methods used to select patients in the matched cohort Noted that the indirect comparison was of trial data for ibrutinib compared with data from a non-trial setting (real world evidence) for Physician choice

- **Is this range of hazard ratios for PFS of ibrutinib vs alternative care clinically plausible?**

Progression free survival: comparison of ibrutinib vs standard care from TA491

[redacted]

Key committee conclusions on clinical effectiveness from TA491

Topic	Committee conclusions
High unmet need	**Current treatment options include combining rituximab with chemotherapy**. Repeated chemotherapy limited by cumulative toxicity. Treatment options can rapidly become exhausted ~ibrutinib is a novel treatment with a different mechanism of action
Comparator	**"Physician's choice" (PC) of standard therapy.** Included blend of alternative 2nd line rituximab/chemotherapy options.
Clinical effectiveness of ibrutinib	**Single arm data** **Data from Study 1118E immature** but ibrutinib associated with high response rates and high progression-free survival and overall survival rates at 2 to 3 years. Longer-term effects on progression and survival uncertain because **no long term data.**
	Indirect comparison **Ibrutinib appears more clinically effective than existing treatment, but uncertainty regarding long-term PFS and survival benefit because of limitations in available data**

Updated clinical data for CDF review

Trials:		
Study 1118E **(n=63)**	**Median follow up:** Previously **37 months, now 59 months**	Outcomes collected: Time to treatment discontinuation (TTD); PFS; OS
iNNOVATE **(n=31)**	**Median follow up:** Previously **17 months, now 57.9 months**	Outcomes collected: TTD; PFS; OS; Pre-progression mortality (PPM)
New since TA491: real-world non-comparative data for ibrutinib:		
SACT database **(n=823)**	NHS England electronic clinical data collection over 3 years for people with WM having received at least 1 prior therapy before ibrutinib. **Median follow-up of 12.9 months.** Outcomes collected**:** TTD,OS and On treatment mortality (OTM)	
National Rory Morrison Registry (RMR) (**n=112**)	Clinical registry started 2017: data from existing/new patients with WM in the UK **n>500**). Patients having ibrutinib as 2nd or subsequent-line considered in CDF review (n=112). **Median follow-up of XXXX months.** Outcomes collected: TTD,PFS, OS, PPM and OTM	
Estimate of treatment effect of ibrutinib vs. Physicians choice on progression free survival		
Company uses **original estimate from TA491** of the hazard ratio for PFS with ibrutinib vs. Physicians choice (XXX). Provides alternative matched adjusted indirect comparison using updated data from Study 1118E with data from European chart review (HR XXXX).		

Physicians choice (PC); Pre-progression mortality (PPM); On treatment mortality (OTM); Time to treatment discontinuation (TTD);

Summary of patient characteristics of updated and new evidence

Differences in baseline characteristics across all 4 studies:

- Company consider SACT most generalisable to UK clinical practice
- People in Study 1118E younger and have less severe disease than people in the SACT dataset
- People in the Rory Morrison registry (RMR) on average older than Study 1118E patients
- People in iNNOVATE (people refractory to rituximab) more heavily pre-treated and considered to have a poorer prognosis than those in Study 1118E and SACT

Baseline characteristics			Source: Table 4 (page 19 of ERG report)	
	Updated evidence		**New evidence**	
	Study 1118E	iNNOVATE arm C	SACT	RMR
Age (median, years)	63 (range 44-86); (mean, 64.5)	67 (range 47-90)	75 (range NR)	XXXXXXXX
Eastern Cooperative Oncology Group (ECOG) performance status				
≤1	63 (100%)	25 (81%)	469 (57%)	XXXXXX
≥2	-	6 (19%)	132 (16%)	XXXXXX
Missing	-	-	222 (27%)	XXXXXX
Number of previous lines of treatments				
Median	2	4	NR	XXXXXX
Range	1 to 9	2 to 6	NR	XXXXXX

- **Is SACT the most appropriate source of data for the efficacy of ibrutinib and generalisable to how it would be used in future?**

CDF Review – terms of engagement * key issues

Subject	Data collection agreement	Company Adherent/departing from terms of engagement
Population	Adults with WM who have had at least 1 prior therapy	✓
Comparator	Clinical and cost-effectiveness evidence for ibrutinib should be presented compared to Physicians Choice	✓
Comparative Effectiveness *	Explore appropriate comparison based on data collected during managed access period~ can use iNNOVATE data to inform relative effectiveness of ibrutinib compared with standard of care	✗ updating ITC with iNNOVATE data would increase uncertainty due to small sample size; ITC not updated
Survival data*	Use more mature, PFS and OS data using data collected through SACT, Study 1118E, iNNOVATE and the Rory Morrison Registry (RMR) – established 2017.	? Model type means OS curves from updated data not directly used in model (but ibrutinib modelled OS calibrated using SACT data) ? PFS for ibrutinib in SACT cohort estimated by applying TTD to PFS hazard ratio from RMR, to SACT TTD Data from iNNOVATE Arm C presented as supportive evidence
Pre-progression mortality*	Use data collected through SACT, more mature data from Study 1118E and iNNOVATE to inform pre-progression mortality (PPM) Time to progression rather than time to subsequent treatment should be used to calculate PPM.	? SACT estimate for on-treatment mortality (proxy for pre-progression mortality with ibrutinib) used in base-case analysis

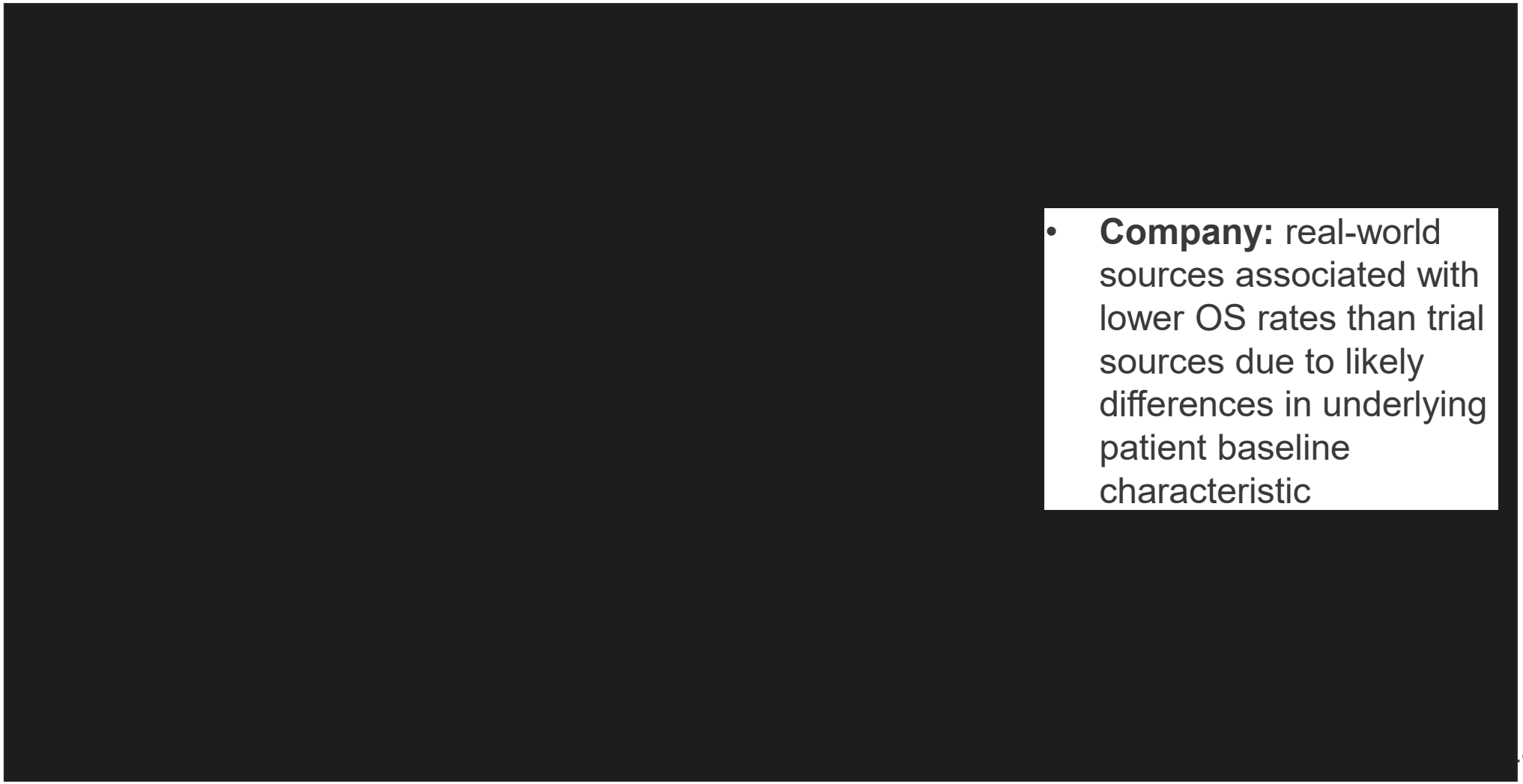
Updated progression free survival: ibrutinib
(PFS is key driver in the model)

- Updated PFS data from Study 1118E and iNNOVATE Arm C as well as new evidence from the RMR dataset for those with one or more prior treatments
- No PFS data from SACT : **therefore this has to be calculated from other sources**

- Higher rates of progression observed in the Rory Morrison registry (RMR) cohort than Study 1118E.
- **ERG**: Differences in patient characteristics between studies may explain apparent differences in PFS outcomes between the available sources

Updated overall survival: ibrutinib

- Updated OS data from all 4 sources; median OS not reached in any
- At 24 months, proportion of patients still alive was 95% and XXXXXin Study 1118E and iNNOVATE Arm C, respectively, versus XXXXXand 73% in the Rory Morrison registry and SACT datasets, respectively



- **Company:** real-world sources associated with lower OS rates than trial sources due to likely differences in underlying patient baseline characteristic

Relative effectiveness of ibrutinib PFS versus Physician's choice (PC) of alternative

- Company CDF review submission did not update estimate from TA491. ITC of study 1118E vs. subgroup of ECR gave a HR for PFS of XXX (95% confidence interval [CI] XXxxxxxxX.
- After technical engagement, the company updated TA491 indirect treatment comparison with additional Study 1118E long-term data using a matching-adjusted indirect comparison (MAIC) with the full dataset from the European Chart Review. Updated HR based on 59-month follow-up is XXXXXXXXXXXXXXXXXXX
- Company considers original TA491 estimate is most appropriate (used in new base-case).

	TA491 ITC	MAIC
HR for ibrutinib vs Physicians choice	XXXX	xxxxx
Study 1118E follow-up duration (median months)	24	59
Patient level data available?	Yes	No
Methodology	Matching, multivariable Cox Regression Analyses	MAIC

ERG:

- MAIC is useful in providing supporting evidence of the relative treatment effect on PFS for ibrutinib versus Physician choice
- Company approach does not rely on assuming proportional hazards as log cumulative hazards plots suggest violation of proportional hazards assumption~ not explored by company due to time limitations
- Important to consider if HR for PFS in the model produces plausible predictions of PFS and OS for patients receiving standard care of Physician's Choice

Key clinical issues

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2) The company's hazard ratio for progression free survival for ibrutinib vs standard care as used in TA491 was XXXXX, based on a comparison of the progression free survival from study 1118E compared with matched patients from an observational European chart study. Is this figure clinically plausible, and transferable to this Cancer Drugs Fund review?

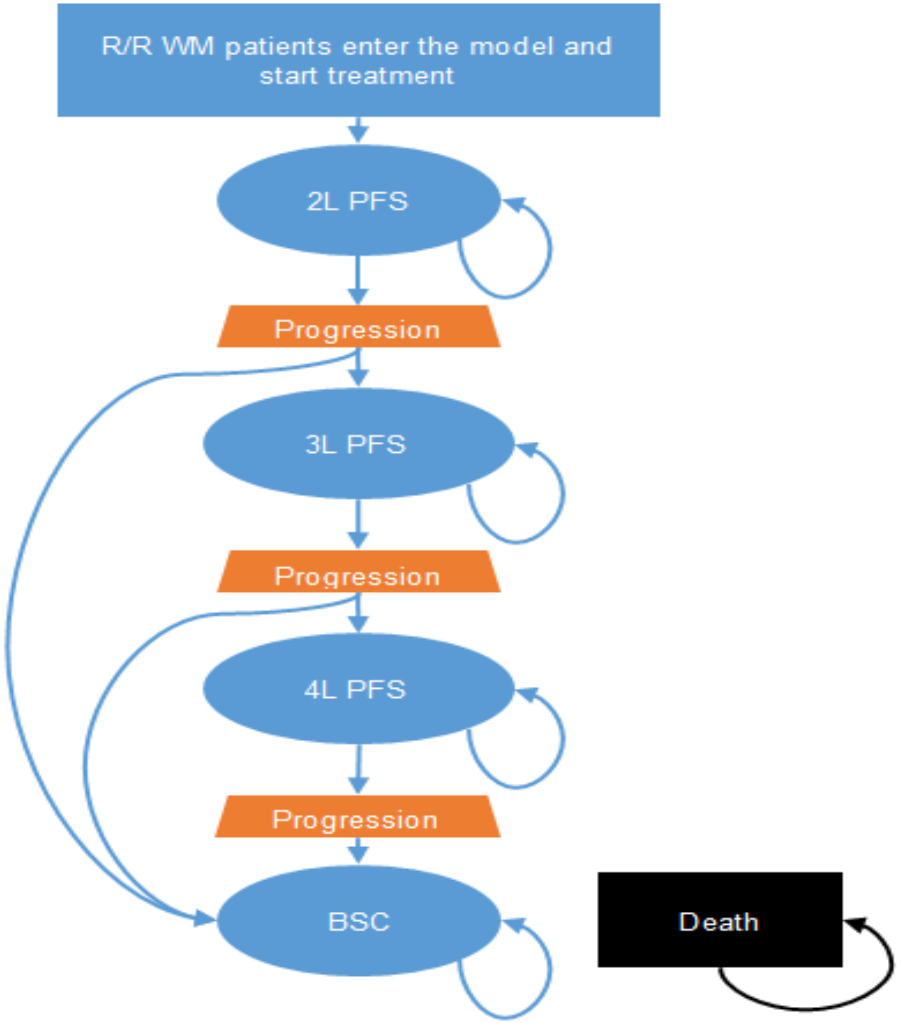
Cost effectiveness

Key cost effectiveness issues

1) Given that SACT does not record progression data, what is the most appropriate approach to estimating PFS with ibrutinib
2) How does stopping treatment relate to disease progression? TA491 model assumed PFS=TTD (i.e.no patients stopped before progression or continued post progression)
3) Is the current approach suggested by the ERG of indirectly estimating PFS from TTD data from SACT (accepted by the company) reasonable? (if PFS = TTD, ICER increases but if PFS = time to subsequent treatment, ICER decreases)
4) The hazard ratio for PFS vs standard care is major model driver:
   - Company revised base-case includes hazard ratio of XXXXXXX
   - What is the best estimate of PFS benefit: is the new matched adjusted indirect comparison using hazard ratio of XXXXX (from 59 month follow up from Study 1118E) reasonable?
   - If the hazard ratio is higher than this (difference in PFS smaller), it has a major effect on the ICER in ERG scenario analyses
5) Is the modelled long term overall survival in the 'physician's choice' [comparator arm] plausible?
   - Potentially a modelling artifact because OS is not modelled directly and treatment effect applied to ibrutinib arm.
6) What is the committee's view of the plausibility of modelled outcomes from the revised company/ERG base-case which gives an ICER above the range considered cost effective?

Economic model used in TA491

	TA491 model
Modelled cohort patient characteristics	Study 1118E
Transition probabilities	
PFS-Physicians choice	HR from ITC applied modelled ibrutinib arm
PFS – ibrutinib	Study 1118E
PPM – ibrutinib	Age- and sex-adjusted life tables 2012-2014
PPM – Physicians choice	ECR without censoring for progression events
Probability 3L → 4L treatment	European Chart Review
PPS 3L and 4L treatment and post-progression survival on BSC	European Chart Review
Probability of receiving 3L or 4L treatment	Expert opinion
TTD – ibrutinib	Assumed equal to PFS
TTD – Physicians choice	



Note: Model driver is 2nd line time to progression which is modelled to differ between ibrutinib and 'physicians choice' using data from ITC. All subsequent transition probabilities same in each modelled arm

NICE

PFS, progression free survival; PC physician's choice; PPM, pre-progression mortality; PPS post-progression survival; TTD, time to treatment discontinuation; HR, Hazard ratio; ITC, indirect treatment comparison; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care

Key committee conclusions from TA491: cost effectiveness

Topic	Committee conclusions
Model structure	Markov, 5 health state transition model was **acceptable for decision-making.**
Modelling pre-progression mortality	Considerable uncertainty in estimating pre-progression mortality (important because long time spent pre-progression due to disease trajectory): • Potential inflated risk of death before progression in comparator group (Physician choice) • Estimates unclear for people on ibrutinib as half of patients with WM die from unrelated causes. Pre-progression survival expected to be better due to complications associated with alternative long term chemotherapy **Company approach acceptable but representative of "best-case scenario"** **Yielded ICER of £54,000 per QALY, but commercial agreement in CDF at cost effective price**
End of Life	Life expectancy is over **24 months and end of life criteria not met.**

Updates included in new company base case

Parameter	TA491 model	Company CDF base case model (after technical engagement)
Modelled patient characteristics	Study 1118E	SACT (+ 1118E for body surface area)
PFS-Physicians choice	Hazard ratio from indirect treatment comparison applied to modelled ibrutinib arm	Unchanged
PFS – ibrutinib	Study 1118E	Indirectly estimated from TTD data from SACT
PPM – Physicians choice	European Chart Review (ECR) without censoring for progression events	European Chart Review considering only deaths during PFS
PPM – ibrutinib	Age- and sex-adjusted life tables 2012-2014	Parametric model fitted to the death while on-treatment Kaplan-Meier data from SACT
PPS 3L and 4L treatment and post-progression survival on BSC	European Chart Review	Adjustment factor applied to post-progression mortality risks from European Chart Review by calibrating modelled OS against SACT OS data
TTD – ibrutinib	Assumed equal to PFS	Exponential model fitted to data on treatment duration from SACT
TTD – Physicians choice		Assumed equal to PFS

Updates to adverse event frequency and some costs; all other modelling assumptions unchanged

NICE

PFS, progression free survival; PC physician's choice; HR hazard ratio; PPM, pre-progression mortality; PPS post-progression survival; TTD, time to treatment discontinuation; OS, overall survival; ITC, indirect treatment comparison

Estimating ibrutinib PFS in SACT cohort: agreed approach

Company:

- SACT PFS data not collected. Does not consider TTD good proxy for PFS : although no time to event PFS data collected in SACT, 67% stopped treatment before progression
- TTD reported in both SACT and Rory Morrison registry (RMR), PFS only reported in RMR
- In original post CDF base case, data from RMR used to derive the modelled PFS for the SACT cohort using a hazard ratio derived between RMR treatment duration and SACT treatment duration; this HR then applied to RMR PFS to produce SACT "derived" PFS

ERG:

- More appropriate to estimate PFS for the ibrutinib group by assuming a proportional relationship between TTD and PFS in RMR based on a comparison of the exponential survival models fitted to this data (HR=1.17) and then applying this HR to the TTD model fitted to SACT data. Gives more plausible modelled outcomes than company approach
- This approach rests on 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)
- If consider PFS=TTD, the ICER increases. If PFS= time to subsequent treatment, ICER decreases

Company technical engagement response

- Company accepts ERG preferred analysis of combining SACT and RMR data in a different way to estimate ibrutinib PFS improves face-validity of its original base-case results and includes in its revised base-case.

PFS, progression free survival; PC physician's choice; HR hazard ratio; TTD, time to treatment discontinuation; Rory Morrison registry (RMR)

Calibrating modelled OS to SACT OS: agreed approach

Company:

- SACT OS data not used directly in model because of model type
- Post-progression mortality risk estimated from the European Chart Review calibrated so that the model predicts OS for the ibrutinib group consistent with the SACT data

ERG:

- Considered a calibration appropriate to reflect expected OS in clinical practice in the model based on SACT data, but suggested alternative method to do this to minimise differences between observed and model-predicted overall survival

Company technical engagement response

- Company updated its approach to the ERG suggestion after technical engagement to improve face-validity of its original base-case results and includes in its revised base-case.

Pre-progression mortality (PPM): agreed approach

Company:

Pre-progression mortality – 2nd line treatment with ibrutinib

- Company base case model initially used PPM estimate based on 24-month data-cut of Study 1118E from TA491- 3 deaths
- Evidence from SACT and Rory Morrison registry suggests XXX died on treatment with ibrutinib.
- Rory Morrison registry data indicates XXXX of patients died prior to progression.

Pre-progression mortality – 2nd line treatment with Physicians choice

- Pre-progression mortality for Physicians choice group based on same parametric survival model as in TA491.
- Company used a log-normal survival distribution fitted to data on PPM for patients receiving 2nd, 3rd or or 4th -line treatment in the ECR.
- PPM risks capped by age- and sex-adjusted mortality risks for the general population based on UK life tables 2017-19: mortality risks increase with age in both treatment groups.

ERG:

- Using available 'on-treatment death' data from SACT more consistent with modelled population, but this may be an underestimation if treatment discontinuation precedes progression
- ERG's clinical expert considered PPM risk in SACT population would be higher than in Study 1118E because of differences in age leading to a higher risk of other-cause mortality
- PPM for ibrutinib set equal to the on-treatment mortality rate from SACT in ERG preferred base-case analysis

Company technical engagement response

- Company accepts ERG preferred analysis for PPM with ibrutinib of using a parametric model fitted to the on-treatment death KM data from SACT improves face-validity of its original base-case results and includes in its revised base-case.
- PPM for Physicians choice remains unchanged from TA491

Pre-progression mortality (PPM)Rory Morrison registry (RMR)

Company base case results (deterministic)

During technical engagement the company updated the assumptions its base case to use the ERG preferred assumptions

Analysis	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Revised company base-case: ERG preferences	2.88	XXXX	XXXX	XXXXXX
Scenarios around assumptions on relative treatment effect of ibrutinib vs. PC on PFS (company base case HR for PFS ibrutinib vs. PC; HR= XXX)				
Revised company base-case with MAIC; HR for PFS =XXX	2.80	XXXX	XXXX	XXXXXX
ERG: assumed HR for PFS = 0.50	2.34	XXXX	XXXX	XXXXXX
ERG: assumed HR for PFS = 0.75	1.78	XXXX	XXXX	XXXXXX
Note: * Undiscounted. PC: Physicians choice				

Expert opinion on plausibility of model predictions at technical engagement

Model prediction	Clinical expert 1 (ERG)	TE response (clinical expert 2)	TE response (clinical expert 3)
(a) Ibrutinib group: Gap between TTD and PFS **Company's approach pre-technical engagement (TE) ~1 years; post-TE ~ 6 months**	Patients usually stay on treatment until the point of progression, and those who discontinue before that point progress soon after treatment is stopped.	Agrees with clinical expert 1	5-10% will stop ibrutinib before progressing due to intolerance. No lag between stopping ibrutinib and progressing. Patients progressing whilst on ibrutinib may remain on ibrutinib because of ongoing clinical benefit and no indication for next line of therapy
(b) Ibrutinib group: Gap between PFS and OS **Company's approach pre-TE 0.41 years; post-TE ~1 year**	At least two thirds of patients who progressed respond to salvage therapy after ibrutinib for at least 3-4 years.(Gustine *et al*, 2018) reports a response rate of 71% and a median OS of 21-32 months after ibrutinib discontinuation.	Agrees with expert 1 that gap [of ~6 months] is not considered to be plausible and that patients who progress on ibrutinib are sometimes salvageable on 3rd line and 4th line chemotherapy.	Median time between PFS and OS is *"a lot longer"*. As seen from RMR and published real world data, patients can still achieve good responses with repeated lines of chemoimmunotherapy, although the duration of response may be shorter compared with 1st-line.
(c) Physicians choice group: Expected % died at 6 years **Company's approach pre-TE 99.4% ; post-TE 97.6%**	At 6 years, the proportion of surviving patients on Physician choice would be half of that for patients on ibrutinib.	Company's prediction that virtually all Physician choice-treated patients die by 6 years after starting initial treatment for relapsed/refractory WM is unrealistic as some patients survive beyond 6 years	More people will be alive at this time point as demonstrated by European Chart Review

Company base-case/ERG preferred model predicted outcomes: potential lack of face validity?

Mean undiscounted time in years for TTD, PFS, PPS and OS

Model-predicted outcome	TA491 model		Company CDF model post technical engagement	
	Ibrutinib	Physicians choice	Ibrutinib	Physicians choice
TTD	3.80	1.46	3.24	0.80
PFS	3.80	1.46	3.71	0.80
PPS	4.16	3.16	1.16	1.18
OS	7.96	4.62	4.86	1.98

Source: amendment of table 16 of ERG report provided by ERG as an addendum to company technical engagement response

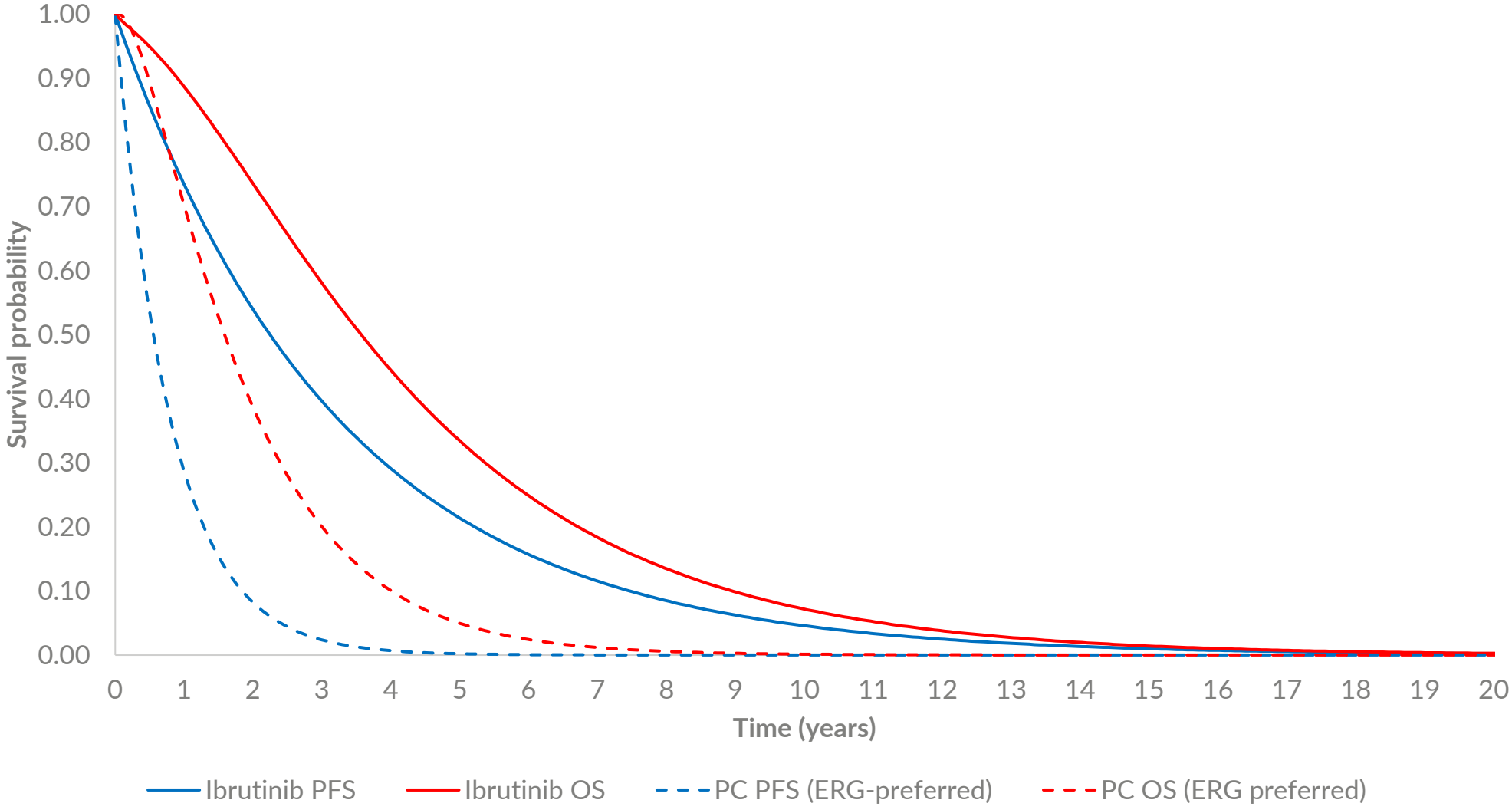
Revised company base-case/ERG preferred analyses now predicts:

- a ~6 month delay before progression with ibrutinib when people discontinue treatment
- a ~1 year delay from progression until death (ibrutinib and Physician choice)
- 97.6% of people in the and Physician choice arm dead at 6 years

Are these estimates clinical plausible?

TTD, time to treatment discontinuation; PFS, progression free survival; PPS post-progression survival; OS, overall survival

Company base-case/ERG preferred model predicted survival outcomes for ibrutinib and and Physician choice arms

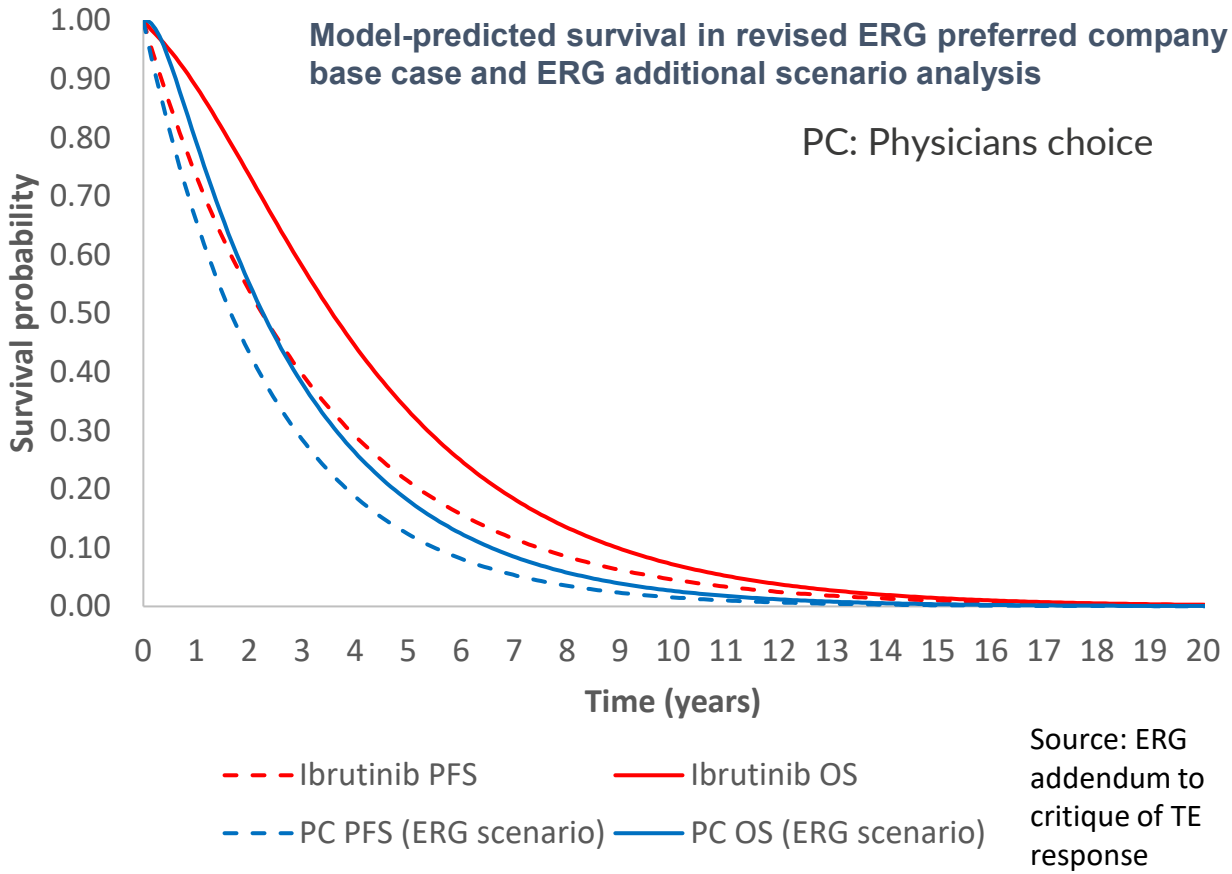


Source: ERG addendum to critique of TE response

Additional ERG scenario analysis

ERG:

- ERG clinical expert suggested that at 6 years, the probability that a patient initiating Physician choice treatment for relapsed/refractory WM would be half of that for patients receiving ibrutinib
- The company's model predicts a 6-year OS probability for patients on ibrutinib of 25%. The ERG notes that the key parameter which drives OS for patients on Physician choice is the HR from the indirect treatment comparison.
- ERG calculated the HR required in order for the model to predict a 6-year OS probability for Physician choice of 12.5% calculated (estimated to be 0.74)



Source: ERG addendum to critique of TE response

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Revised company base-case (ERG preferred analysis)							
Ibrutinib	4.86	[redacted]	[redacted]	2.88	[redacted]	[redacted]	[redacted]
PC	1.98	[redacted]	[redacted]	-	-	-	-
Additional scenario analysis assuming 6-year OS for PC equals 50% of 6-year OS for ibrutinib							
Ibrutinib	4.86	[redacted]	[redacted]	1.81	[redacted]	[redacted]	[redacted]
PC	3.05	[redacted]	[redacted]	-	-	-	-

Key cost effectiveness issues

1) Given that SACT does not record progression data, what is the most appropriate approach to estimating PFS with ibrutinib
2) How does stopping treatment relate to disease progression? TA491 model assumed PFS=TTD (i.e.no patients stopped before progression or continued post progression)
3) Is the current approach suggested by the ERG of indirectly estimating PFS from TTD data from SACT (accepted by the company) reasonable? (if PFS = TTD, ICER increases but if PFS = time to subsequent treatment, ICER decreases)
4) The hazard ratio for PFS vs standard care is major model driver:
   - Company revised base-case includes hazard ratio of XXXX
   - What is the best estimate of PFS benefit: is the new matched adjusted indirect comparison using hazard ratio of XXX (from 59 month follow up from Study 1118E) reasonable?
   - If the hazard ratio is higher than this (difference in PFS smaller), it has a major effect on the ICER in ERG scenario analyses
5) Is the modelled long term overall survival in the 'physician's choice' [comparator arm] plausible?
   - Potentially a modelling artifact because OS is not modelled directly and treatment effect applied to ibrutinib arm.
6) What is the committee's view of the plausibility of modelled outcomes from the revised company/ERG base-case which gives an ICER above the range considered cost effective?

Spare slides

Estimating expected Ibrutinib PFS in SACT cohort: time-to-next-treatment (TTNT)

Technical engagement response

- Clinical experts have suggested people with relapsed/refractory WM treated with ibrutinib switch treatment shortly after they progress, ibrutinib TTNT data can provide an upper boundary for ibrutinib SACT PFS.
- Company independently commissioned analyses from Public Health England (PHE) on ibrutinib time-to-next-treatment (TTNT) in SACT
- SACT cohort show median TTNT of XXXX months (95% CI: XXXXXXX)
- median TD is 24.9 months in the final SACT report.
- **Scenario analysis:** KM data for TTNT fitted with six standard parametric models.(exponential curve selected)
- Extrapolated TTNT assumed to represent PFS for ibrutinib.

ERG:

- Agrees that scenario analysis using TTNT data from SACT as a proxy for PFS likely provides an upper bound for PFS
- Company model assumes XXXXX of patients do not receive active subsequent-line treatment and receive BSC alone; TTNT in SACT likely overestimated.
- Scenario useful in providing an estimate of the lower bound for ICER; true PFS will lie somewhere between TTD and TTNT

Company scenarios around approach to estimate expected PFS in SACT cohort

During technical engagement the company updated the assumptions its base case to be the same as the ERG preferred assumptions

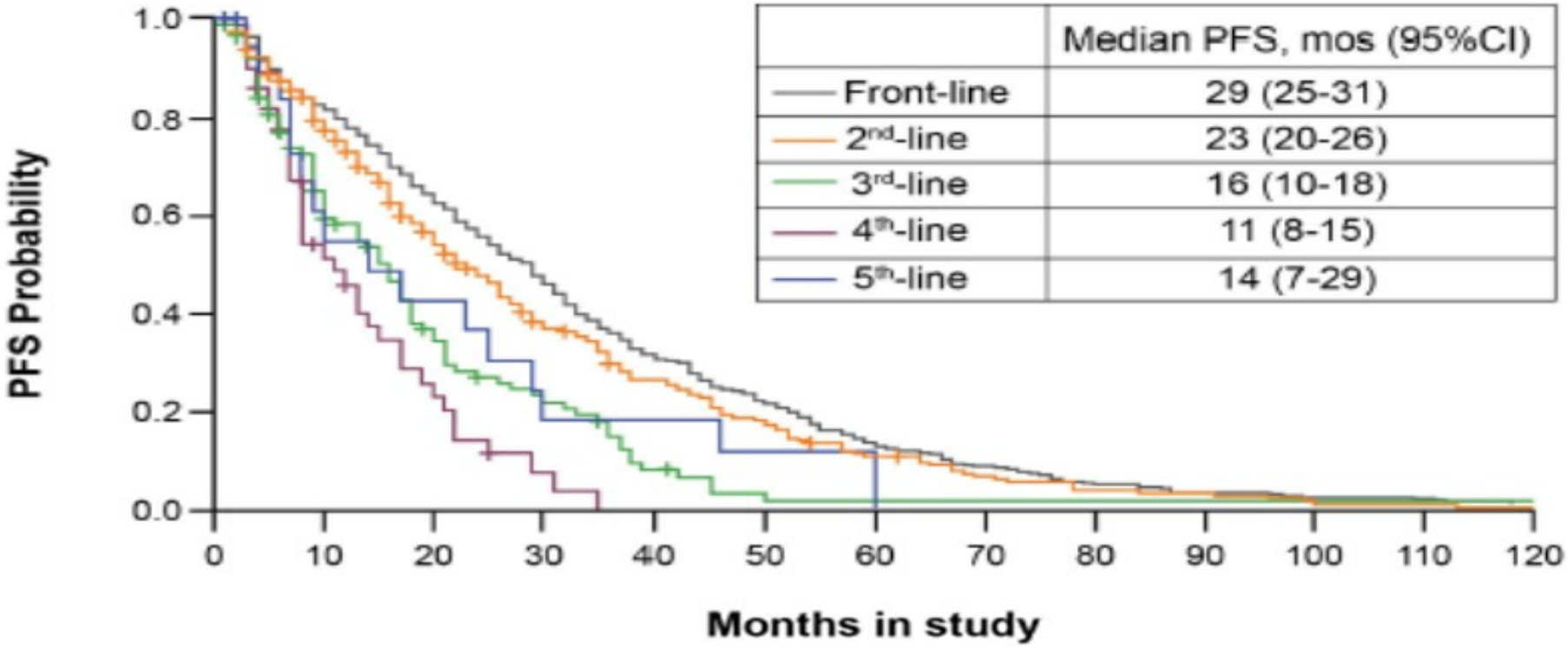
Company scenarios around approach to estimate expected PFS in SACT cohort

During technical engagement the company updated the assumptions its base case to be the same as the ERG preferred assumptions

Analysis	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Revised company base-case	2.88	XXX	XXXXXXX	XXXXXXX
Scenarios around approach to estimate expected PFS in SACT cohort				
ibrutinib PFS = TTNT (SACT)	4.85	XXX	XXXXXXX	XXXXXXX
ERG: assume PFS = TTD	2.05	XXX	XXXXXXX	XXXXXXX
Note: * Undiscounted.				

Progression free survival: Comparator Physician choice evidence from European chart review

Kaplan-Meier PFS estimates by line of treatment

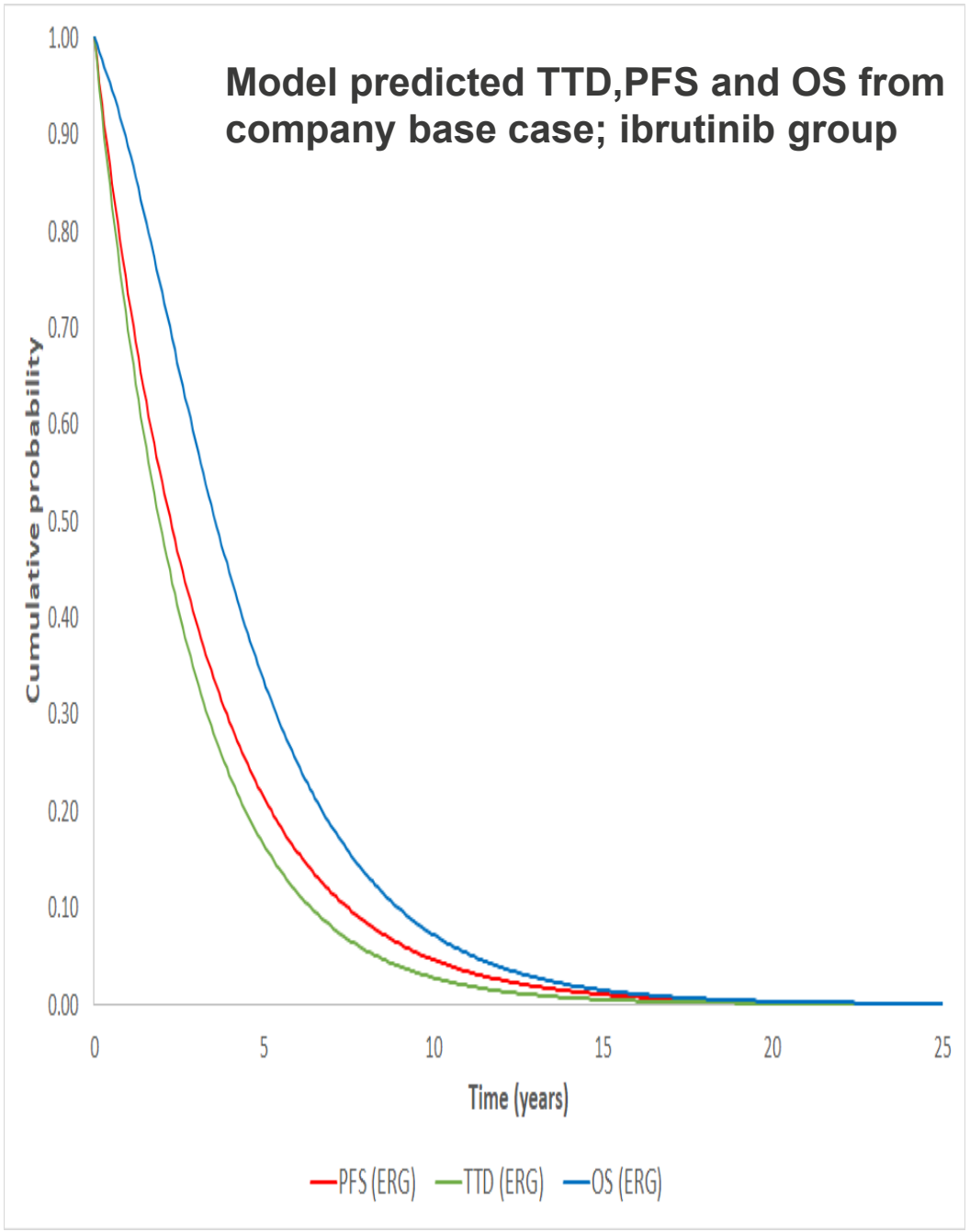


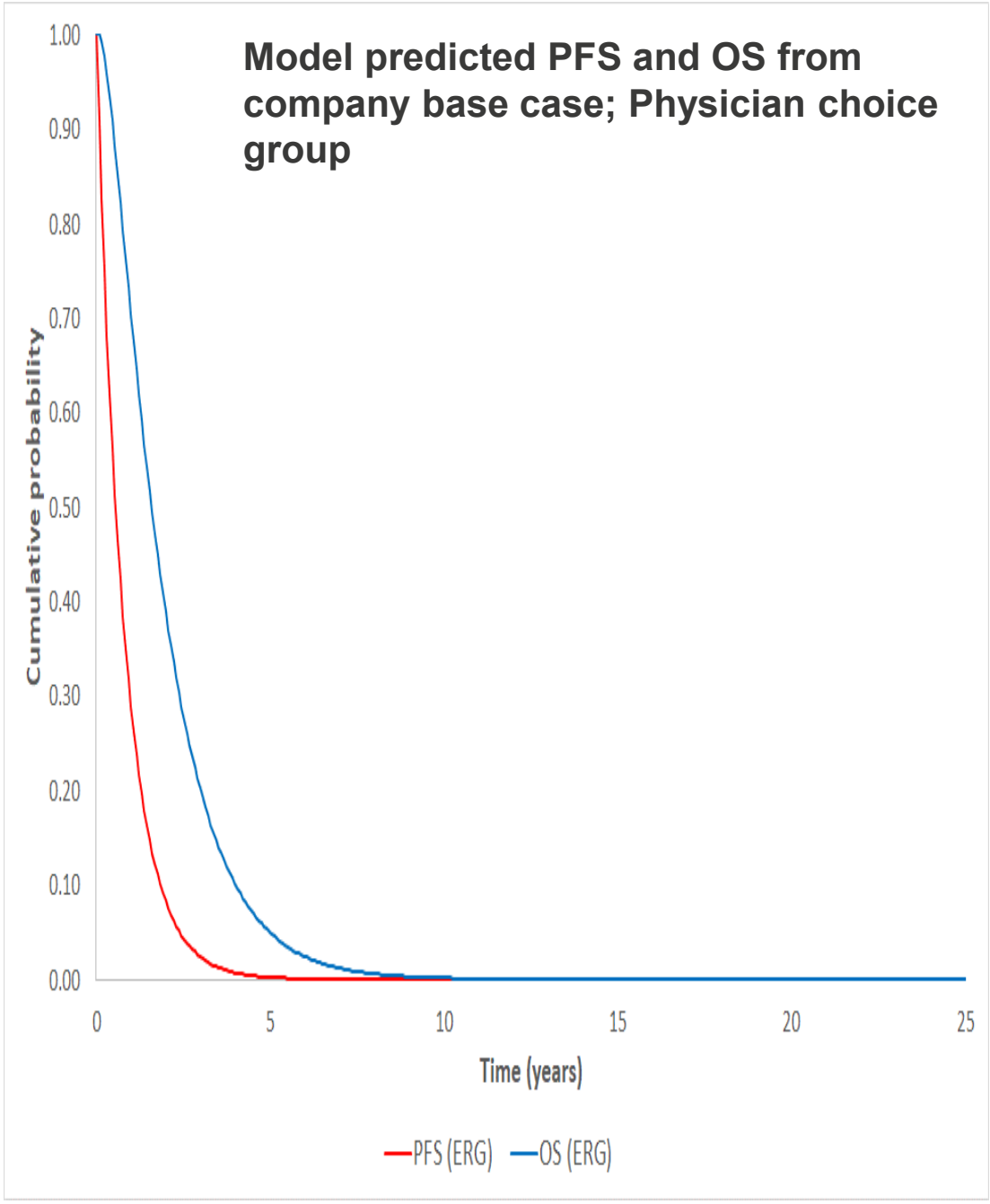
	Median PFS, mos (95%CI)
Front-line	29 (25-31)
2nd-line	23 (20-26)
3rd-line	16 (10-18)
4th-line	11 (8-15)
5th-line	14 (7-29)

Number at risk													
Front-line	454	376	293	218	145	101	63	40	25	16	12	11	6
2nd-line	387	189	118	76	51	35	20	12	7	6	3	12	1
3rd-line	160	58	30	18	6	2	1	1	1	1	1	1	1
4th-line	61	20	9	2	0	0	0	0	0	0	0	0	0
5th-line	26	10	7	4	3	2	2	0	0	0	0	0	0

Source: TA491 committee slides

Company base-case/ERG preferred model predicted outcomes:





Source: Fig 14 and 15 of ERG report