Ruxolitinib for treating polycythaemia vera

Public observer slides – ACIC information redacted

Technology appraisal committee D [12 July 2023] – 2nd appraisal committee meeting

Chair: Dr Stephen Smith

Lead team: Carole Pitkeathley, Dr Ivan Koychev, Giles Monnickendam

External assessment group: Southampton Health Technologies Assessment Centre

Technical team: Alice Pritchard, Owen Swales, Lizzie Walker, Jasdeep Hayre

Company: Novartis Pharmaceuticals

Recap from 1st committee meeting

Ruxolitinib not recommended for treating polycythaemia vera: • **company's model and long-term treatment effect estimates are highly uncertain** • **all ICERs were above the cost-effective range**	
Managed access (CDF)	Not suitable
Equalities issues	None identified
Outstanding uncertainties identified by committee	• Most appropriate model structure • Long term treatment effect on overall survival • Preferred extrapolation for time to treatment discontinuation

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost-effectiveness ratio; IMF, innovative medicines fund

Key issues from ACM1

Key issue and committee conclusions at ACM1	Resolved?	ICER impact
Generalisability: MAJIC-PV is most appropriate source of clinical-effectiveness evidence for decision making	Resolved at ACM1	
Model structure: A disease-state progression model is preferred, but would need to see: • Probabilistic results with committee preferred assumptions • Full independent clinical assessment • Validation of the model results compared to MAJIC-PV and registry data	For discussion at ACM2	Large
Uncertainty around the long-term effect of ruxolitinib on overall survival: • Both the constant and time-varying HR are highly uncertain • Would like to see full probabilistic sensitivity analysis • Scenario analysis using an overall survival HR equal to 1	For discussion at ACM2	Large
Treatment waning: Treatment waning should be included in OS modelling	Resolved at ACM1	
Treatment discontinuation: Cannot determine a preferred extrapolation distribution because this would likely be affected by change to model structure	Not relevant with new model	Small
Utility estimates: EQ-5D was the most appropriate utility measure	Resolved at ACM1	

Abbreviations: ACM, appraisal committee meeting; HR, hazard ratio; OS, overall survival

Background on polycythaemia vera

RECAP

Causes

- Polycythaemia vera (PV) is a bone marrow disease caused typically by a change in the JAK2 gene that leads to an increase in the number of blood cells in the blood

Epidemiology

- PV can affect people of any age, but is most prevalent in men and people aged over 60
- UK prevalence is approximately 6.8 per 100,000

Diagnosis, symptoms and prognosis

- Diagnosis via blood test to check red blood cell count or haematocrit level
- Symptoms include headaches, blurred vision, red and/or itchy skin, tiredness, high blood pressure, dizziness, confusion, bleeding problems, and gout
- Lower life expectancy due to increased risk of blood clots, an enlarged spleen (splenomegaly), scarring of bone marrow (myelofibrosis) and acute myeloid leukaemia

Abbreviations: JAK2, janus kinase 2; PV polycythaemia vera

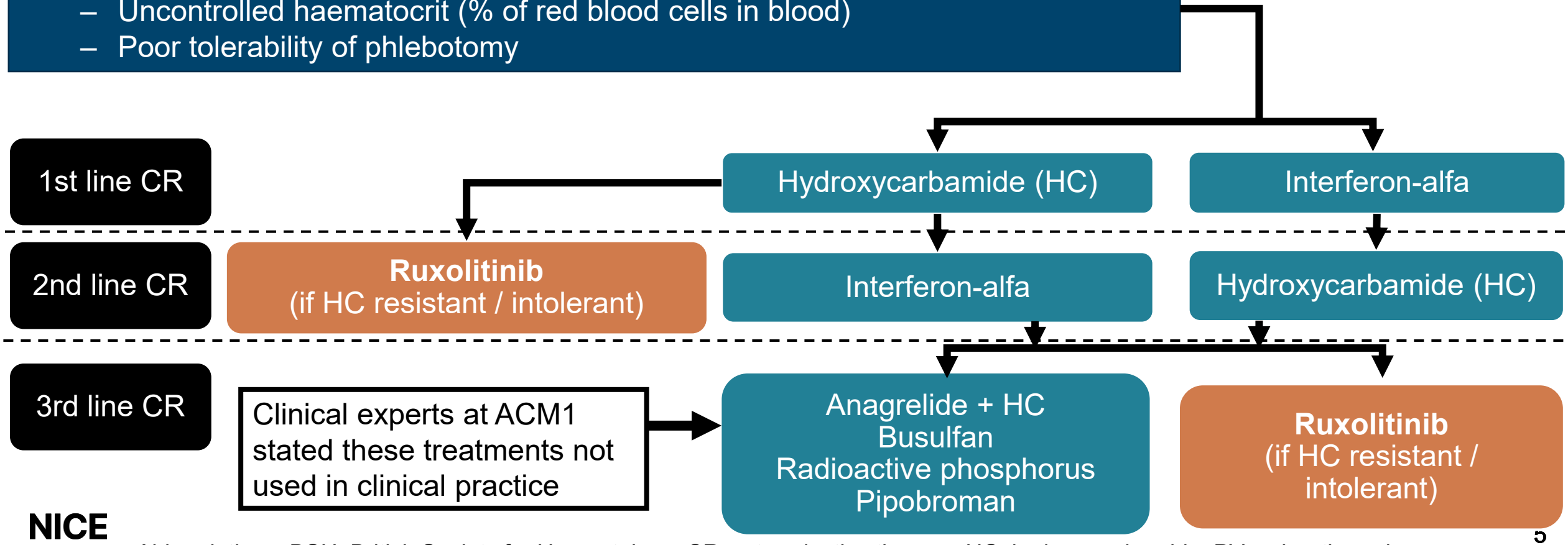
RECAP

Treatment pathway

Ruxolitinib could be given to people who are intolerant to hydroxycarbamide

Figure: Recommended treatment pathway for people with PV (BSH 2018 guidelines)

- Phlebotomy + low dose aspirin to maintain HCT < 0.45
- Cytoreductive therapy (CR) is recommended for:
  - High-risk (people ≥ 65 years and/or with a history of thrombosis)
  - Uncontrolled haematocrit (% of red blood cells in blood)
  - Poor tolerability of phlebotomy



NICE

Abbreviations: BSH, British Society for Haematology; CR, cytoreductive therapy; HC, hydroxycarbamide; PV, polycythaemia vera

Ruxolitinib (Jakavi, Novartis Pharmaceuticals)

RECAP

This appraisal is a review of TA356 – NICE was previously unable to make a recommendation for ruxolitinib because no evidence submission was received

Table: Technology details

Marketing authorisation	• MHRA license has been granted: ruxolitinib is indicated for the treatment of adults with PV who are resistant or intolerant to HC
Mechanism of action	• PV is associated with aberrant activation of JAK1/2 signalling pathways • JAK1/2 are involved in signalling pathways of cytokines and growth factors needed for the formation of blood cells and immune function • Ruxolitinib is a selective inhibitor of the JAK enzymes, specifically the competitive inhibition of the ATP-binding catalytic site on JAK1/2
Administration	• Ruxolitinib is self-administered as an oral tablet • Recommended dose of ruxolitinib is a 10mg tablet taken twice daily
Price	• List price for ruxolitinib of £2,856 per 56 pack of 10mg tablets • A simple patient access scheme discount is available for ruxolitinib

Abbreviations: ATP, adenosine triphosphate; HC, hydroxycarbamide; JAK, janus kinase; MHRA, Medicines and Healthcare products Regulatory Agency; PV, polycythaemia vera

Key clinical trials

RECAP

Table: Clinical trial designs and outcomes for RESPONSE, RESPONSE-2 and MAJIC-PV

	RESPONSE*	RESPONSE-2*	MAJIC-PV
Design	Open label phase 3 RCT	Open label phase 3 RCT	Open label phase 2 RCT
Population	Adults with PV R/I to HC and **have splenomegaly**	Adults with PV R/I to HC and **no splenomegaly**	Adults with **high-risk PV** R/I to HC
Intervention	Ruxolitinib	Ruxolitinib	Ruxolitinib
Comparator	Best available therapy	Best available therapy	Best available therapy
Duration	256 weeks	260 weeks	260 weeks
Key outcomes	HCT control, spleen volume at week 32, CHR, response durability	HCT control at week 28, CHR	CHR at 1 year, partial response, survival
Locations	19 countries, 3 UK sites	12 countries, 0 UK sites	UK only, 38 UK sites

*Crossover to ruxolitinib permitted at 28 weeks (RESPONSE-2) and 32 weeks (RESPONSE)

Abbreviations: CHR, complete haematological response; HC, hydroxycarbamide; HCT, haematocrit; PV, polycythaemia vera; RCT, randomised controlled trial; R/I, resistant or intolerant to

Consultation responses to draft guidance (1)

Comments received from:

- Novartis Pharmaceuticals
- Clinical experts (who attended ACM1)
- Leukaemia Care
- MPN Voice

Abbreviations: MPN, myeloproliferative neoplasm

Consultation responses to draft guidance (2)

Summary of responses

Uncertainty in overall survival

Clinical experts:

- None of the trials showed statistically significantly improved OS with ruxolitinib, but this is a high bar in PV due to there being a long baseline survival
- In MAJIC-PV, ruxolitinib:
  - Significantly improved event-free-survival
  - Significantly reduced thromboembolic events and numerically reduced transformation events
    → Thromboembolic events and transformation are associated with worse long-term survival
    Thrombosis it the main cause of death for people with PV
  - Significantly improved OS in people treated with ruxolitinib who had a molecular response (defined as 50% reduction of driver mutation VAF)
- Prolonged OS with ruxolitinib versus best available therapy (BAT) is plausible

Leukaemia Care and MPN Voice:

- PV is rare, it is not possible to conduct large enough trials which investigate OS with certainty, therefore ruxolitinib is disadvantaged in standard HTA process
- Uncertainty in data does not mean there is not an OS benefit

Abbreviations: BAT, best available therapy; EFS, event free survival; MPN, myeloproliferative neoplasm; OS, overall survival; PV, polycythaemia vera; VAF, variant allele frequency

Consultation responses to draft guidance (3)

Summary of responses

Unmet need

Clinical experts, Leukaemia Care and MPN Voice:

- There is an unmet need for additional therapies in hydroxycarbamide-intolerant PV
- This group of people are faced with difficult choices for treatment options, for example, busulfan may increase risk of leukaemia several fold

Factual inaccuracy: Cause of itching

Clinical experts:

- No relationship between itch and white cell count
- The aetiology of itch is not clearly understood in PV

Abbreviations: MPN, myeloproliferative neoplasm; PV, polycythaemia vera

Equality considerations

Equality considerations

- No equality issues were identified by the committee
- In responses to draft guidance, MPN Voice stated that there was a potential inequality issue due to PV being rare and this limits the size of the trials and brings in uncertainty regarding OS benefit
    - Disease rarity is not a protected characteristic in equalities legislation
    - However, the committee will be mindful that evidence generation may be particularly difficult in rare diseases
    - The committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition affects the ability to generate high-quality evidence before applying greater flexibility.

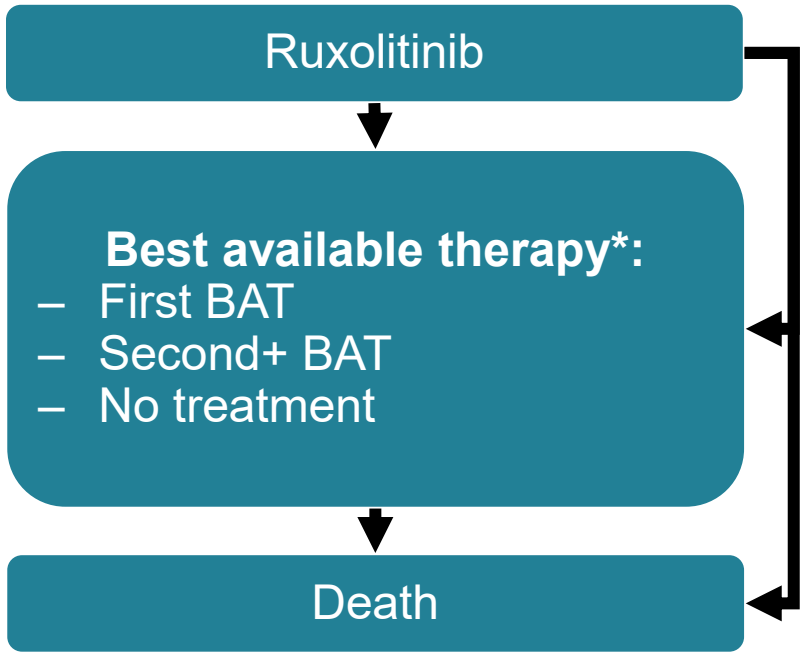
Abbreviations: OS, overall survival; MPN, myeloproliferative neoplasm

RECAP

Key issue: Company's model structure

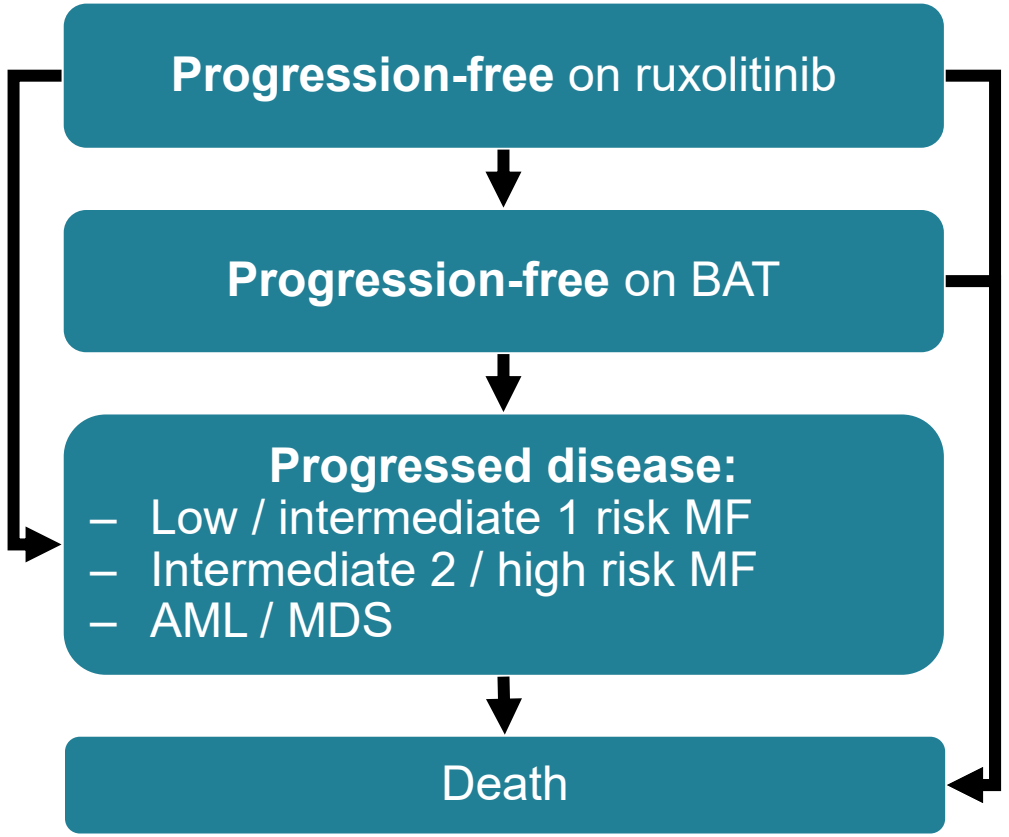
Committee preferred a disease-state progression model with their preferred assumptions

Original company model



*Substates for RESPONSE/-2 populations only

New company model (progression-based model)



Abbreviations: AML, acute myeloid leukaemia; BAT, best available therapy; MDS, myelodysplastic syndrome; MF, myelofibrosis; PFS, progression-free survival; STM, state transition model

Key issue: Model structure (1)

Is the disease-state progression-based model appropriate for decision making?

Draft guidance

- A progression-based model is preferred. The committee would want to see full validation of the model and probabilistic results using an updated progression-based model which reflect committee preferences

Company draft guidance response

Provided the committee with a disease progression-based model which included:

- Committee preferred assumptions
- Probabilistic results
- Clinical validation and validated model against external data

Clinical validation with 10 clinical experts in a virtual advisory board:

- Concluded inputs and assumptions were reasonable

Validation of model results against external data:

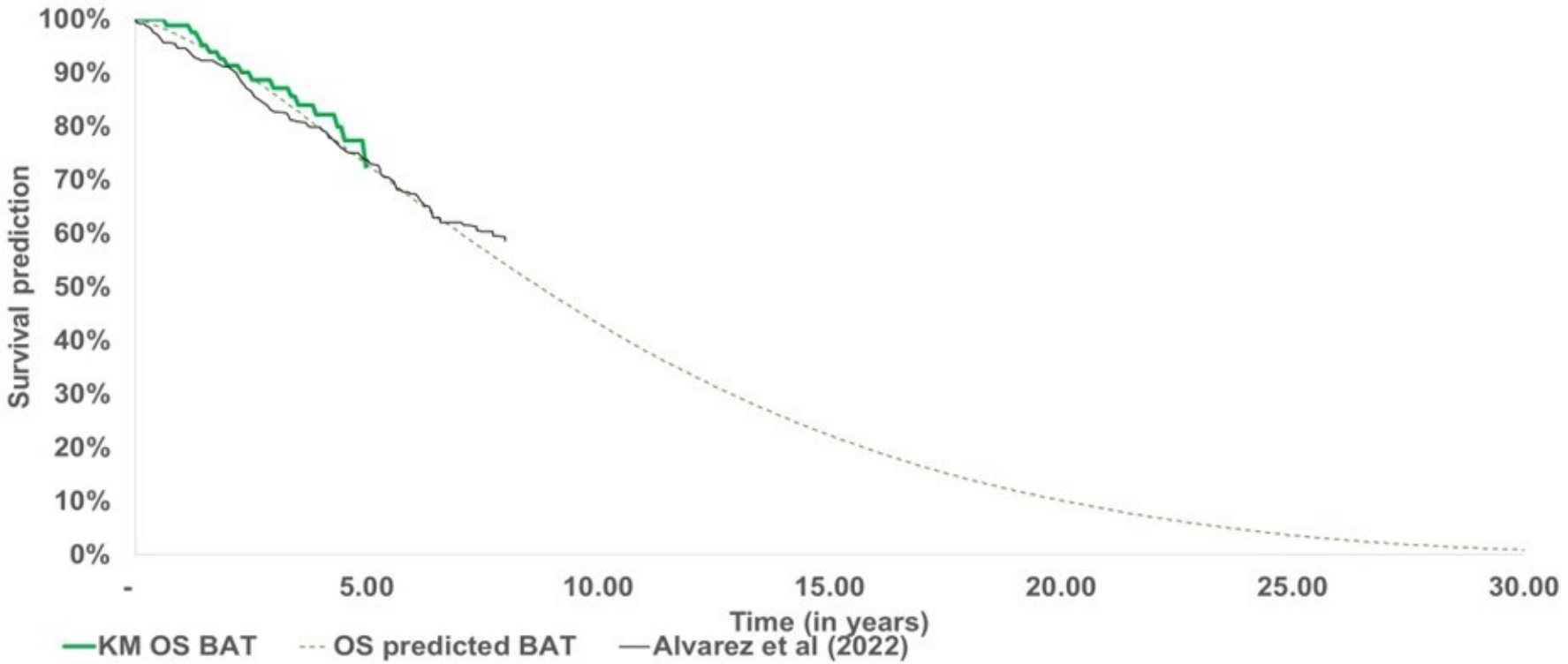
- Conducted targeted search to identify studies reporting survival of people with PV that is R/I to HC/HU
- Only 2 studies were relevant and reported long-term survival of patients with BAT R/I to HC/HU
- The study reporting larger cohort and follow up was used, Alvarez et al (2022) (**see next slide**)

Abbreviations: BAT, best available therapy; HC, hydroxycarbamide; PV, polycythaemia vera; R/I, resistant or intolerant to

Key issue: Model structure (2)

Model validation with external data from GEMFIN registry

Figure: Comparison of model predictions for BAT and OS in Alvarez et al (2022)



Company draft guidance response

Survival reported in Alvarez et al (2022) compared with survival reported in the MAJIC-PV trial

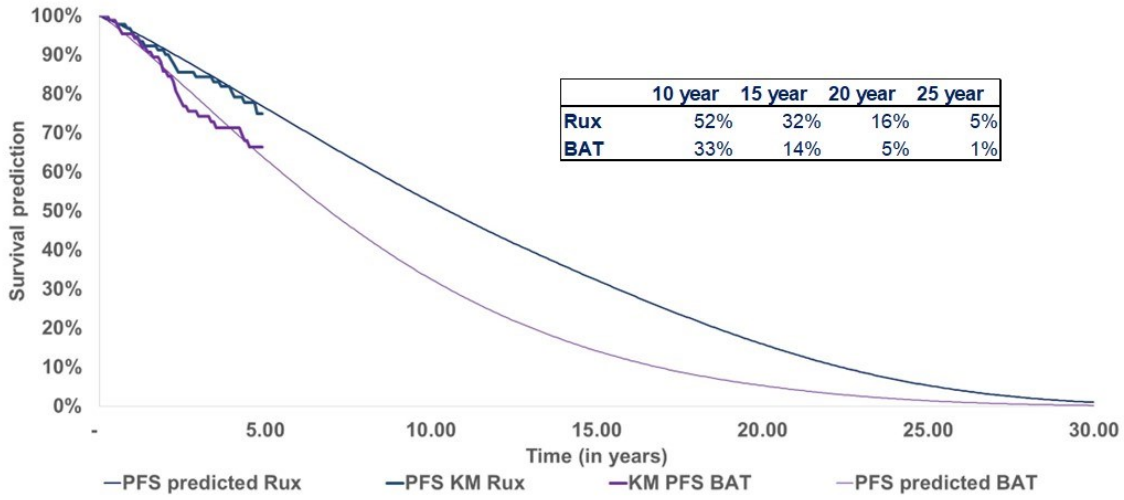
Alvarez et al (2022) included 272 patients with PV resistant or intolerant to HC treated with BAT from the Spanish Registry of Polycythemia Vera, sponsored by GEMFIN

Abbreviations: BAT, best available therapy; KM, Kaplan-Meier; OS, overall survival; PV, polycythaemia vera

Key issue: Model structure (3)

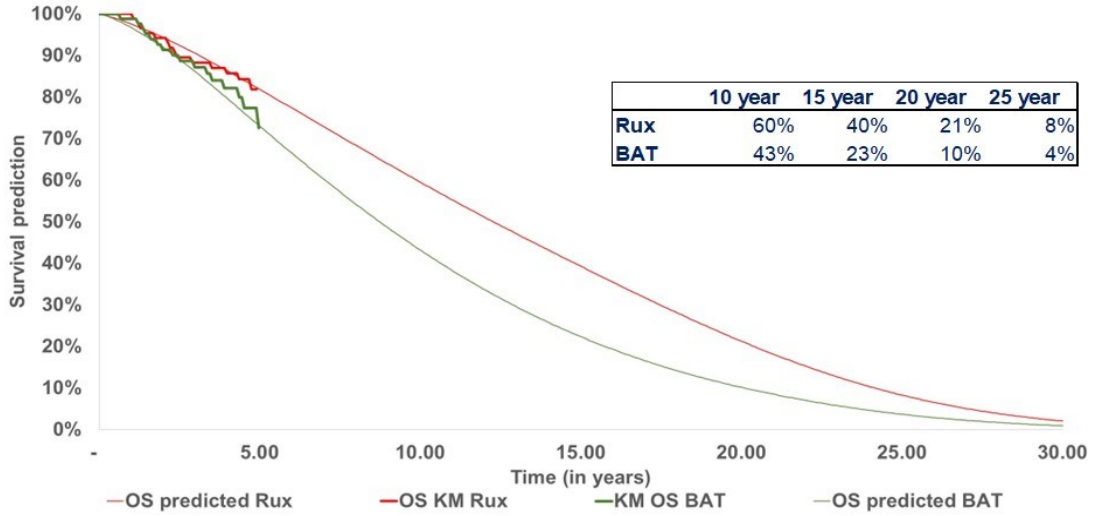
Comparison of model predictions from progression-based model with PFS and OS from MAJIC-PV

Figure: Comparison of model predictions and observed PFS in MAJIC-PV



	10 year	15 year	20 year	25 year
Rux	52%	32%	16%	5%
BAT	33%	14%	5%	1%

Figure: Comparison of model predictions and observed OS in MAJIC-PV



	10 year	15 year	20 year	25 year
Rux	60%	40%	21%	8%
BAT	43%	23%	10%	4%

Company draft guidance response

Model predictions for PFS and OS were generally aligned with observed data from the trial at 5 years

EAG comments

- OS and PFS predictions have reasonable fit to the trial results, given variation in the KM curves
- MAJIC-PV trial was not powered for the PFS and OS outcomes and number of deaths and incidence of MF and AML/MDS were low

Abbreviations: AML, acute myeloid leukaemia; BAT, best available therapy; EAG, evidence assessment group; HR, hazard ratio; KM, Kaplan-Meier; MDS, myelodysplastic syndrome; MF, myelofibrosis; OS, overall survival; Rux, ruxolitinib; TE, technical engagement

Key issue: Model structure (4)

EAG still note uncertainty in model inputs but note no alternative data

EAG comments

Clinical validation conducted by company

- Based on the number of centres covered by clinical experts included, it is likely that experts are representative of those which manage PV in the NHS
- 6 of the 10 clinical experts used for clinical validation were authors of MAJIC-PV trial, the company did not report conflicts of interests for the clinical experts
- The company did not declare the number of experts which agreed or disagreed with each of the issues discussed and did not mention if those who were agreeing had potential conflicts of interest
- EAG conclude that the clinical validation exercise conducted by the company did not reduce uncertainty around validity and plausibility of model inputs

Validation of model results against external data

- EAG identified issues with the company's targeted searches for survival data in people with PV
- However, EAG conducted their own targeted searches and did not find any additional external data sources and no clinical experts were aware of better or alternative data sources
- So is it likely that all sources of external data have been identified

Abbreviations: EAG, evidence assessment group; PV, polycythaemia vera

Key issue: Model structure (5)

Inputs	Progression-based model	EAG comments
Baseline info	MAJIC-PV trial	Committee preferred approach at ACM1
Definition of progression	PFS outcome in MAJIC-PV trial: transformation to MF, MDS, AML or death from any cause	• Agree with definition on progression • Survival impact of thromboses/bleeds may not be fully captured, could underestimate benefit of ruxolitinib
Progression free survival	Time spent in PFS states governed by: • **Pre-progression survival (PrePS):** mortality prior to transformation • **MF-free survival (MFS):** time from baseline to fibrotic transformation to MF • **Leukaemia-free survival (LFS):** time from baseline to transformation to AML or MDS Curves adjusted to fit estimated 5-year probability of event from MAJIC-PV For BAT, company used 5-year estimate of MF/AML from Alvarez-Larrán (2022) (5.69%), as experts considered MAJIC-PV estimate (1.67%) was low	• **PrePS**: change in HR for mortality estimated by fitting distributions to PFS KM curve from MAJIC-PV, Weibull used despite 3 other distributions having better but very similar statistical fit • **Time to transformation (MFS and LFS)**: Weibull distributions fitted to KM curves from Szuber (2019); no justification given but visual fit is reasonable • **LFS**: Using lower probability of AML estimated from MAJIC-PV (rather than Alvarez-Larrán) results in a more favourable LFS curve for BAT

Abbreviations: AML, acute myeloid leukaemia; EAG, evidence assessment group; KM, Kaplan-Meier; MDS, myelodysplastic syndrome; MF, myelofibrosis; OS, overall survival; PFS, progression free survival

Key issue: Model structure (6)

Input	Progression-based model	EAG comments
Post-progression survival	OS extrapolations based on transformation: • **AML**: Weibull distribution fitted to survival data for a US cohort of PV patients (Tang 2017) • **Low/intermediate-1 risk MF**: Weibull curve fitted to KM data for the intermediate-1 risk group from Tefferi (2019), adjusted with HR from Cervantes (2009) for low risk • **Intermediate-2/high risk MF**: OS estimates taken from TA386, assuming 23% of people receive ruxolitinib (Mead 2022)	• **AML**: Company do not justify the selection of this source • **Low/intermediate-1 risk MF**: Source for the OS estimates in this subgroup is not clearly stated as Tefferi (2012) was reference provided • **Intermediate-2/high risk MF**: No comments
TTD	Modelled using a hazard ratio for TTD compared with PFS HR estimated from MAJIC-PV KM curves for TTD and PFS	Agree with approach as HR uncertainty is captured in PSA
Other complications	Same as original model with addition of multiplier to adjust for increasing incidence of thromboembolism with age	Removing the multiplier has a very small impact on the ICER
Utilities	Aligned with committee preference for EQ-5D	Checked and verified where possible but could not check confidential data used from TA836
Costs and resource use	Costs based on disease transformation: AML/MDS, Low/intermediate-1 risk MF, Intermediate-2/high risk MF	

Is the disease-state progression model appropriate for decision-making?

Abbreviations: AML, acute myeloid leukaemia; EAG, evidence assessment group; KM, Kaplan-Meier; MDS, myelodysplastic syndrome; MF, myelofibrosis; OS, overall survival; PFS, progression free survival

Key issue: Long-term treatment effect on OS (1)

Company's draft guidance response sought clinical expert validation

Draft guidance

- Size of the overall survival treatment effect estimated for ruxolitinib compared with best available therapy is highly uncertain
- Uncertain whether constant or time-varying OS HR more appropriate
- The committee would like to see full probabilistic sensitivity analyses exploring HR for OS and scenario analyses presenting more conservative assumptions for survival gain

Company draft guidance response

- Provided scenario analysis when HR is equal to 1 in the original model – leads to large increase in ICER
- Provide two scenario analyses assessing size of treatment effect for OS in progression-based model

Clinical validation with 10 clinical experts in a virtual advisory board:

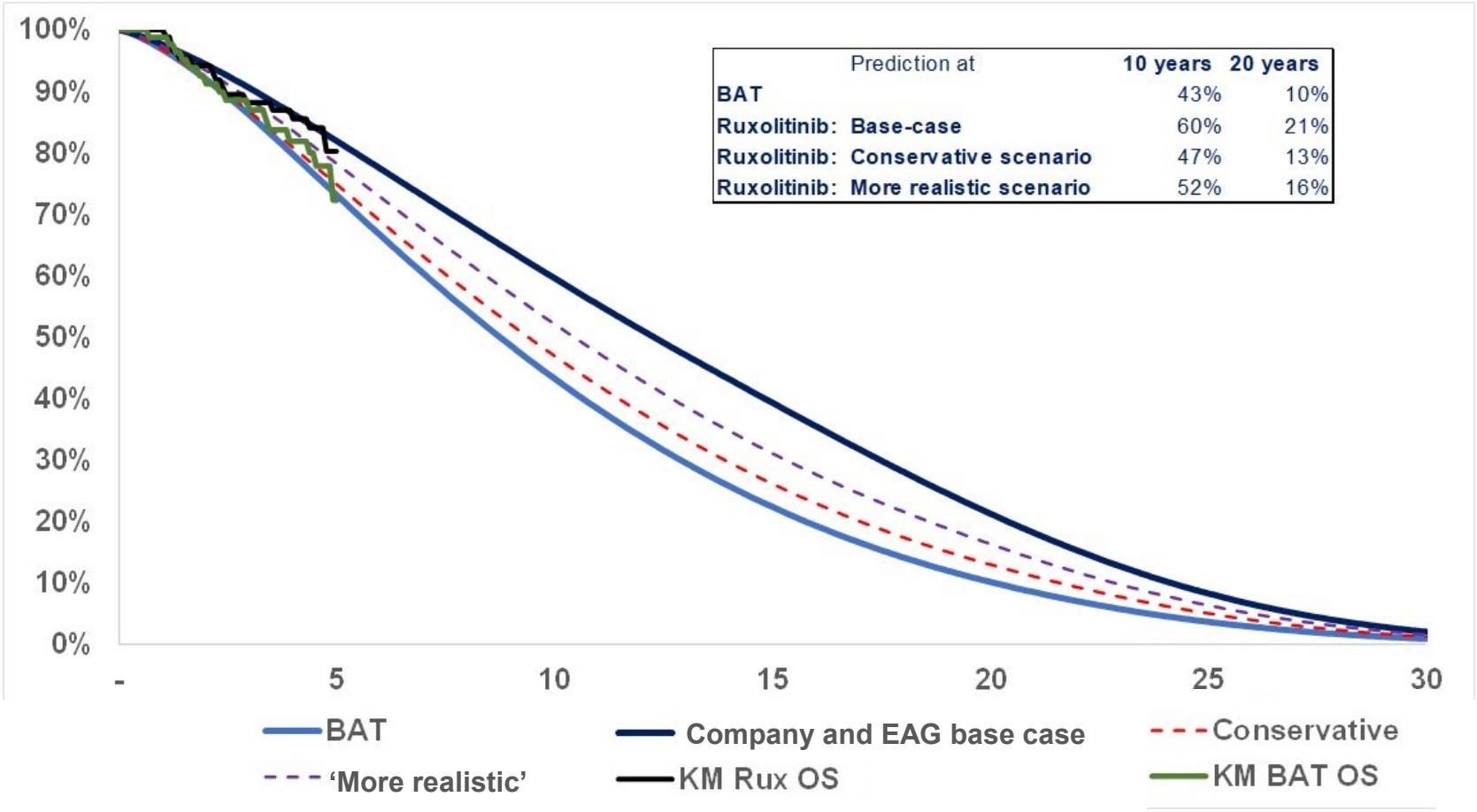
- Some clinical experts found it difficult to comment on model predictions for long term survival
- A consensus that ruxolitinib would be associated with survival gain due to reduced key events and delayed disease progression
- Extent of survival gain unknown due to limited follow up in MAJIC-PV and lack of long-term data

Abbreviations: EAG, evidence assessment group; HR, hazard ratio; OS, overall survival

Key issue: Long-term treatment effect on OS (2)

Scenario analyses assessing long-term treatment effect on OS

Figure: OS predictions for the scenarios using the progression-based model



Company and EAG base case

"More realistic" scenario: Ruxolitinib affects deaths due to reduction in MF and AML/MDS and reduction in other deaths (but not as much as in base case)

"Conservative" scenario: Ruxolitinib only affects deaths due to reduction in MF and AML/MDS

Clinical expert validation:

- Base-case predictions are plausible
- Conservative scenario is extreme due to expected reduction in thrombosis from ruxolitinib use and therefore improvement in survival

NICE

Abbreviations: AML, acute myeloid leukaemia; BAT, best available therapy; EAG, evidence assessment group; HR, hazard ratio; KM, Kaplan-Meier; MDS, myelodysplastic syndrome; MF, myelofibrosis; OS, overall survival; Rux, ruxolitinib; TE, technical engagement

Key issue: Long term treatment effect (3)

Scenario analysis has large impact on ICERs

Stakeholder draft guidance responses

- Clinical experts, MPN Voice: Difficult to capture long-term OS in people with PV

EAG comments

Additional scenarios around the size of treatment effect for OS using progression-based model

- Both 'conservative' and 'more realistic' scenario associated with large increase in ICERs
- 'Conservative' scenario provides reasonable bound on uncertainty over ruxolitinib pre-progression survival
- MAJIC-PV trial showed reduction in thromboembolic events and the 'conservative' scenario excludes an effect on deaths due to thromboses

Is the level of uncertainty associated with long term OS acceptable?

Abbreviations: AML, acute myeloid leukaemia; BAT, best available therapy; EAG, evidence assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MPN, myeloproliferative neoplasm; OS, overall survival

Cost-effectiveness results

ICERs are reported in PART 2 slides due to confidential discounts

Summary of cost-effectiveness results based on currently approved commercial arrangements:

- Company has accepted all EAG's and committee's preferred assumptions
- Company's and EAG's base case ICERs for ruxolitinib versus BAT are **higher for all populations** than what would usually be considered a cost-effective use of NHS resources

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Key issues and scenarios for committee to consider

Committee will consider the following scenarios and uncertainties in Part 2 of the meeting

Table Key issues for committee to consider in decision making

Key issue	Uncertainty	Scenario analysis results in Part 2 slides
Model structure	Is the disease-state progression model appropriate for decision-making?	• Probabilistic results for the progression-based model using committee preferred assumptions
Treatment effect	Which is the most appropriate approach for modelling OS?	• Probabilistic results assuming no survival difference using original model structure. • Additional scenarios around size of treatment effect for OS using progression-based model

Abbreviations: OS, overall survival; TTD, time to discontinuation

NICE National Institute for Health and Care Excellence

Thank you.