Single Technology Appraisal

Ruxolitinib for treating polycythaemia vera (review of TA356) [ID5106]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ruxolitinib for treating polycythaemia vera (review of TA356) [ID5106]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Novartis

2. **Consultee and commentator comments on the Draft Guidance Document** from:
   a. MPN Voice
   b. Leukaemia Care & MPN Voice – joint response.

3. **Comments on the Draft Guidance Document from experts:**
   a. Tim Somervaille, Professor of Haematological Oncology – clinical expert, nominated by Novartis
   b. Claire Harrison, Professor of myeloproliferative neoplasms and clinical director – clinical expert, nominated by Novartis and MPN Voice

There were no comments on the Draft Guidance Document received through the NICE website.

4. **External Academic Group critique of company response to the DG**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 June 2023. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005, Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease [COPD]) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/inhaled corticosteroid (ICS). Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Novartis is disappointed by the draft recommendation from NICE to not recommend ruxolitinib for the treatment of polycythaemia vera (PV) in adult patients who cannot tolerate

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	hydroxycarbamide (HC) (also called hydroxyurea [HU]) or when the condition is resistant or intolerant (R/I) to it.[1] Novartis welcomes the committee's recognition of the clinical benefits of ruxolitinib over best available therapy (BAT) in controlling haematocrit levels, increasing haematological remission, reducing spleen volume (Section 3.4 and 3.6, DGD[1]) and improving event-free survival (reduction in thrombosis, haemorrhage, myelofibrosis [MF], and acute myeloid leukaemia [AML] and myelodysplastic syndrome [MDS]). The committee further recognised that ruxolitinib may improve overall survival (OS) through delaying disease progression (Section 3.12, DGD[1]) and reducing the occurrence of key events (MF, AML/MDS and thrombosis), but that the size of any effect was unknown. The committee further recognised the debilitating nature of PV and the high unmet need for effective therapies that have manageable side effects and improve quality of life, reduce symptoms and survival (Section 3.1, DGD[1]). If the initial decision remains unchanged, PV patients who are R/I to HC/HU will be denied access to an effective treatment option that reduces symptoms, improves quality of life and delays disease progression when compared with current treatments. Novartis is grateful for the opportunity to respond to the Draft Guidance Consultation (otherwise referred to as DGD in this response for simplicity) to address the outstanding questions. Further comments, clarification, and analyses on the remaining uncertainties in the appraisal, as requested by the committee, are provided as part of this response. The committee concluded that the MAJIC-PV trial is the most appropriate trial for decision-making for the full marketing authorisation (Section 3.8 and 3.17, DGD[1]) and therefore all analyses in this response are conducted using data from this trial. The committee further concluded that it preferred the updated progression-based model structure submitted at technical engagement (Section 3.12 and 3.17, DGD[1]), but required further information/analyses, including (Section 3.12 and 3.17, DGD[1]): • Probabilistic results for the updated progression-based model with committee preferred assumptions, including the use of the EuroQol-5 Dimension (EQ-5D) measure. • A full independent clinical assessment. • Validation of the model results compared to MAJIC-PV results and external data including longer-term registry data. In addition to this, the committee requested results using the original model structure for an additional scenario assuming no difference in survival (Section 3.13 and 3.18, DGD[1]). Each of these scenarios and information requested by the committee, alongside clinical validation conducted following the DGD, are presented below. Furthermore, additional scenarios using the progression-based model (see DGD Comment 6) are presented to support the committee in its decision-making. All results in this response are presented probabilistically (based on 2,000 iterations) and incorporate the EAG preferred assumptions when appropriate (e.g., approach for costing Grade

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	1–2 thrombosis for all analyses). Results are also presented using both the EQ-5D (committee-preferred assumption) and Myelofibrosis-8 dimensions (MF-8D) measure as a scenario as acknowledged in the DGD (Section 3.16 and 3.17, DGD[1]). Results presented in this response use the patient access scheme (PAS) discount agreed in TA386 (Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis) in line with the NICE methods guide.[2] [redacted] and demonstrate that ruxolitinib has the potential to represent a cost-effective use of NHS resources.
2	**Base-case probabilistic results using the progression-based model and committee-preferred assumptions.** Probabilistic (deterministic) results using the progression-based model using both the EQ-5D (committee-preferred assumption) and MF-8D (committee-scenario analysis) are presented below in Table 1. **Table 1: Probabilistic (deterministic) results for the progression-based model (using the currently agreed PAS discount for MF)**

Technologies	Total costs (£)	Total LYG*	Total QALYs	Incr. costs (£)	Incr. LYG*	Incr. QALYs	ICER (£/QALY)
Committee-preferred scenario (using EQ-5D)							
Current clinical management	£91,511 (£91,033)	8.14 (8.18)	5.82 (5.88)				
Ruxolitinib	[redacted]	9.82 (10.08)	[redacted]	[redacted]	1.68 (1.90)	[redacted]	[redacted]
Committee-scenario analysis (using MF-8D)							
Current clinical management	£91,827 (£91,033)	8.14 (8.18)	6.18 (6.22)				
Ruxolitinib	[redacted]	9.89 (10.08))	[redacted]	[redacted]	1.75 (1.90)	[redacted]	[redacted]

Footnotes: *indicates results are undiscounted; deterministic results are presented in brackets.
Abbreviations: ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol-5 Dimension; Incr.: incremental; LYGs: life years gained; MD-8D: Myelofibrosis 8 dimensions; MF: myelofibrosis; PAS: patient access scheme; PV: polycythaemia vera; QALYs: quality-adjusted life years.

3	**Full independent clinical assessment of the plausibility of model results and inputs used for the progression-based model.** Clinical validation when developing the progression-based model was obtained at the technical engagement (TE) stage from two of the five clinical experts involved in the validation of the

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	original company submission (CS). The validation included validation of inputs and assumptions (Section 1.2, company's TE response), and included an assessment of the clinical plausibility of model predictions, although Novartis acknowledge that while implied, this was not explicitly stated in the company's response to TE. In response to the DGD, further clinical validation was sought to validate inputs, assumptions, and plausibility of model results. A total of ten clinical experts attended a virtual advisory board held on Tuesday 13th June 2023. This included the five clinical experts involved in the CS (including the two clinical experts that had already provided clinical feedback during TE) and an additional five clinical experts not previously consulted. The five additional clinical experts were identified based on recommendations from the clinical experts already involved, due to their knowledge of PV treatments and management in the NHS. Pre-reading materials were shared prior to the virtual advisory board with the focus on: • Assessing the validity of inputs and assumptions used in the progression-based model. • Assessing the plausibility of model results in terms of prediction for PFS and OS. • Identifying external sources of data that could be used to validate model predictions. • Reviewing the plausibility of scenarios for overall survival. For transparency, the pre-reads, including slides and references, advisory board notes including the list of attendees are provided in the reference pack for this response to the DGD. In summary, acknowledging that there is no perfect source of evidence, there was a consensus that the sources of inputs and assumptions made were reasonable, and no concern was expressed. Some of the clinical experts found it challenging to comment on model predications when considering long-term survival. There was a consensus that ruxolitinib would be associated with a survival gain due to the reduction in key events and delaying disease progression, but some clinical experts stated that the extent of survival gain was unknown and difficult to quantify. Clinical experts also felt that while the predictions under the base-case were plausible they could not confidently reach a consensus due to the limited follow-up in the MAJIC-PV trial and absence of long-term data. Clinical experts noted that patients on ruxolitinib remain on treatment for a long period and they do not expect the treatment effect to wane. The clinical experts also noted that, in the base-case, just over twice as many patients on ruxolitinib (21%) are predicted to be alive at 20 years compared with BAT (10%), which aligns with their previous clinical advice included in the CS but acknowledged the uncertainty in the absence of long-term data. As part of the model validation exercises at the advisory board conducted following the DGD, clinical experts were also shown predictions for a more conservative scenario where the difference between arms is driven by deaths due to MF and AML/MDS only (e.g., same pre-progression mortality - see DGD Comment 6). Clinical experts considered this scenario to be extreme as they expected

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	ruxolitinib to lead to a reduction in thrombosis and therefore an improvement in survival. To aid the committee in its decision, results for this scenario are included in this response to DGD. In summary, clinical experts considered the model predictions under the base-case more likely to be plausible than not but highlighted the uncertainty.

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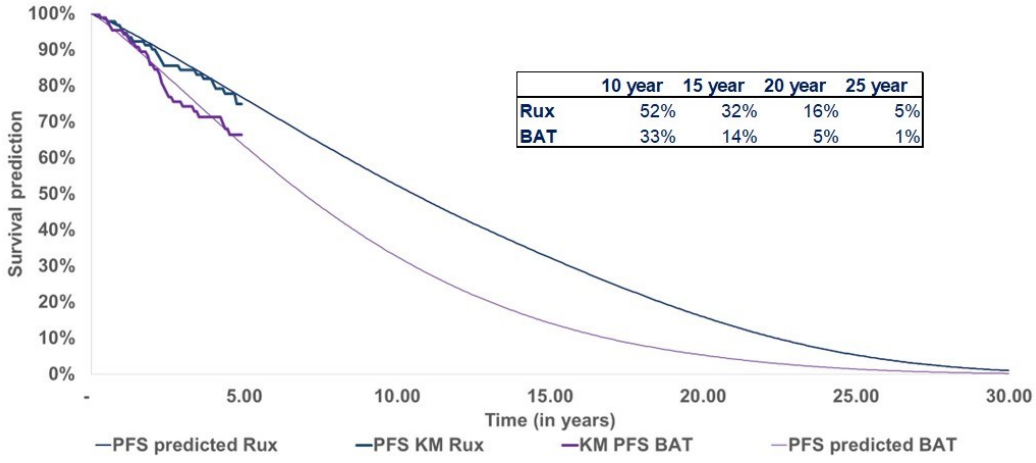
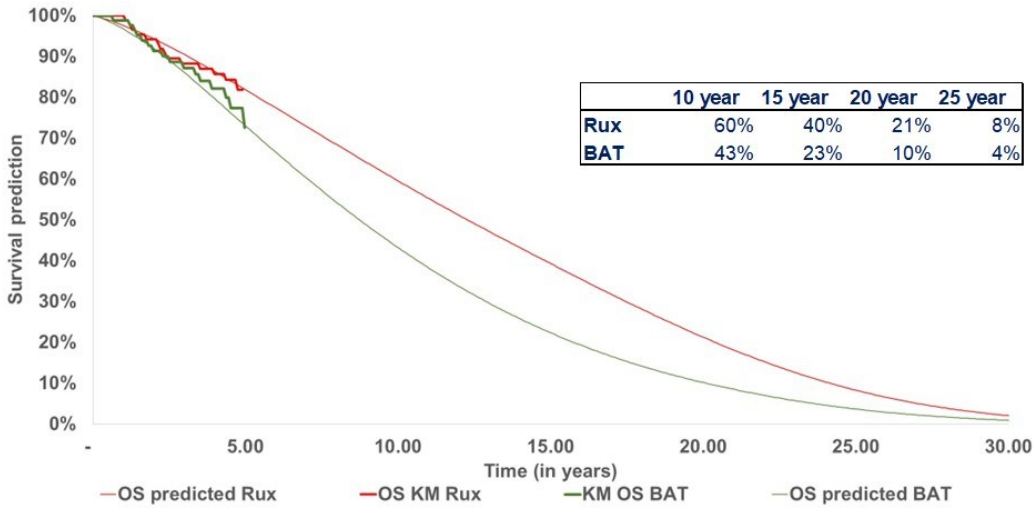
4	**Comparison of model predictions using the progression-based model against the MAJIC-PV results.** The comparison of model predictions against the MAJIC-PV results were previously presented in Novartis' response to TE (Figure 5, company's TE response). This showed that despite the assumptions and use of external data in the model, predictions for PFS and OS were generally aligned with observed data from the trial at 5 years. For transparency, comparisons of model predictions and results from the MAJIC-PV trial are reproduced below in Figure 1 and Figure 2 for PFS and OS, respectively. **Figure 1: 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% **Abbreviations**: BAT: best available therapies; KM: Kaplan–Meier; PFS: progression-free survival; Rux: ruxolitinib. **Figure 2: 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% **Abbreviations**: BAT: best available therapies; KM: Kaplan–Meier; OS: overall survival; Rux: ruxolitinib.

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5	**Validation of model results against external data.** As per the request from the committee to explore the validity of the results against external data, external sources of evidence were identified through a targeted search and through discussion with clinical experts. A targeted search was conducted with the aim to identify studies that report the survival of patients with PV that are R/I to HC/HU. Searches were conducted by an independent reviewer and the search terms and PRISMA diagram are provided in the appendix at the end of this response. A total of 556 studies were screened, of which eight were considered potentially relevant and met the inclusion criteria for the search. Following review, only two studies (from the same author and cohort) were considered relevant and reported on the long-term survival of patients with BAT R/I to HC/HU.[2, 3] This included a recent publication by Alvarez et al. (2022),[2] and the survival from the same cohort that was used for the matched analysis of the RESPONSE-trial (from the same cohort, but less patients and shorter follow-up).[3] Therefore, for the purpose of validation, the study reporting on the larger cohort and follow-up was used. Six studies were not considered further. This included the three primary RESPONSE publications (where BAT OS is confounded by cross-over),[4-6] the MAJIC-PV publication, one publication from Alvarez et al. (2016) that reported the survival from diagnosis rather than at the point of R/I to HC/HU,[7] and finally one study reporting on the short-term survival (2-year) following busulfan (Alvarez et al. 2018) in patients with polycythaemia vera and essential thrombocythemia.[8] In addition to the targeted search, clinical opinion was also sought to identify alternative source of evidence that could be used to validate model predictions. Clinical experts were not aware of other alternative source of evidence, outside those identified through the targeted search. As a result, model predictions for BAT are compared against OS reported in Alvarez *et al.* (2022)[2] in Figure 3. The study included 272 patients with PV R/I to HC/HU treated with BAT from the Spanish Registry of Polycythemia Vera, sponsored by the Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas (GEMFIN). For transparency, the observed OS from the MAJIC-PV is also presented.

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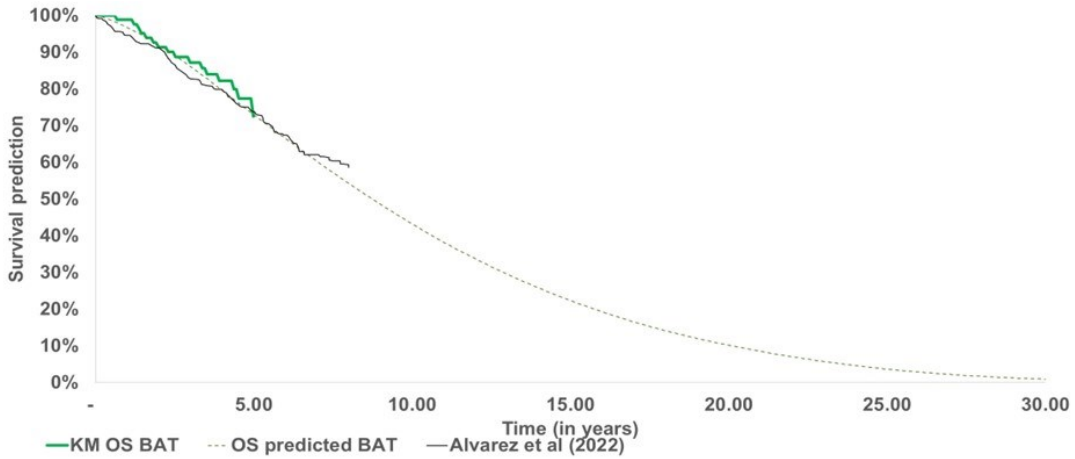
Figure 3: Comparison of model predictions for BAT (progression-based model) and OS reported in Alvarez *et al.* (2022)



Abbreviations: BAT: best available therapies; KM: Kaplan–Meier; OS: overall survival.

As shown in Figure 3, the survival reported in Alvarez *et al.* (2022) was broadly aligned with that reported in the MAJIC-PV trial (Figure 3).[2] Model predictions were aligned with the data in Alvarez *et al.* (2022) despite assumptions and use of external data, providing reassurance of the plausibility of the model results.

5

Scenario requested by the committee assuming no difference in survival using the original model structure.

In addition to further validation and analyses using the progression-based model, the committee requested results of a scenario using an overall survival hazard ratio (HR) equal to 1 in the original model structure (Section 3.18, DGD[1]), i.e. assuming no difference in survival.

Probabilistic (deterministic) results for this scenario are presented below in Table 2, using the EQ-5D (committee-preferred assumption) and the MF-8D (committee-scenario analysis).

Table 2: Probabilistic (deterministic) results assuming no survival difference using the original model structure (using the currently agreed PAS discount for MF)

Technologies	Total costs (£)	Total LYG*	Total QALYs	Incr. costs (£)	Incr. LYG*	Incr. QALYs	ICER (£/QALY)
Committee preferred assumption (using EQ-5D)							
Current clinical management	£83,817 (£83,339)	7.97 (8.02)	5.65 (5.71)				
Ruxolitinib	[redacted]	7.97 (8.02)	[redacted]	[redacted]	0.00 (0.00)	[redacted]	[redacted]
Committee scenario analysis (using MF-8D)							
Current clinical management	£83,995 (£83,339)	8.02 (8.02)	6.08 (6.11)				

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	Ruxolitinib	[redacted]	8.02 (8.02)	[redacted]	[redacted]	0.00 (0.00)	[redacted]	[redacted]

Footnotes: *indicates results are undiscounted; deterministic results are presented in brackets.
Abbreviations: ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol-5 Dimension; Incr.: incremental; LYGs: life years gained; MD-8D: Myelofibrosis 8 dimensions; MF: myelofibrosis; PAS: patient access scheme; PV: polycythaemia vera; QALYs: quality-adjusted life years.

6

Additional scenarios around the size of the treatment effect for overall survival using the progression-based model.

In the DGD, the committee requested a scenario using a hazard ratio for overall survival of 1 using the original model (i.e., no difference in survival between ruxolitinib and BAT). This was because overall survival was modelled directly. As highlighted in the DGD, it is not possible to conduct such a scenario in the progression-based model, as overall survival is modelled as function of PFS where overall survival is driven in part by the incidence of key events (MF and AML/MDS), and pre-progression death estimated from the trial.

Nevertheless, recognising the committee discussion, the uncertainty with the relative effect on survival and to help the committee with its decision-making, results from two alternative scenarios using the progression-based model are reported:

- **A conservative case**: In this scenario, ruxolitinib only affects deaths due to MF and AML/MDS, through a reduction of these events. This scenario was presented to clinical experts during the virtual advisory board and clinical experts considered this scenario to be extreme as they expected ruxolitinib to also lead to a reduction in thrombosis that is expected to lead to an improvement in survival.
- **A more realistic case (predictions in-between the base-case and the conservative scenario)**: In this scenario, ruxolitinib affects deaths due to MF and AML/MDS, through a reduction of these events, but is also associated with a reduction in other death (albeit less than in the base-case). In this scenario, the pre-progression mortality use for the BAT arm is used and adjusted using a hazard ratio so that predictions are in-between those from the base-case and those from the conservative scenario. While this scenario requires some manual adjustment so that predictions are in between the predictions from those in the base-case and those in the conservative scenario, this scenario is presented to aid the committee in its decision-making.

Predictions for OS are shown below in Figure 4 for the different scenarios.

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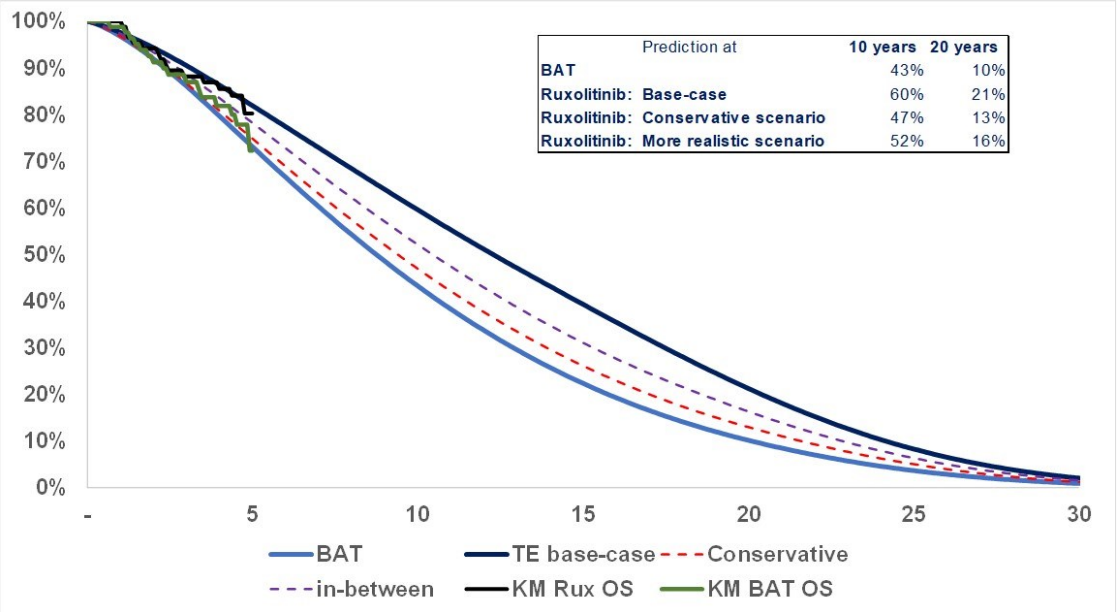
Figure 4: OS predictions for the scenarios using the progression-based model.



Abbreviations: BAT: best available therapies; KM: Kaplan–Meier; OS: overall survival; Rux: ruxolitinib; TE: technical engagement.

Probabilistic (deterministic) results using the committee preferred assumption (e.g. EQ-5D) are presented below in Table 3.

Table 3: Probabilistic (deterministic) results for the additional scenarios using the committee-preferred assumption (e.g. EQ-5D) (using the currently agreed PAS discount for MF)

Technologies	Total costs (£)	Total LYG*	Total QALYs	Incr. costs (£)	Incr. LYG*	Incr. QALYs	ICER (£/QALY)
Conservative case							
Current clinical management	£91,359 (£91,033)	8.14 (8.18)	5.84 (5.88)				
Ruxolitinib	[redacted]	8.52 (8.61)	[redacted]	[redacted]	0.38 (0.43)	[redacted]	[redacted]
More realistic case (in-between)							
Current clinical management	£92,181 (£91,033)	8.21 (8.18)	5.88 (5.88)				
Ruxolitinib	[redacted]	9.18 (9.22)	[redacted]	[redacted]	0.98 (1.04)	[redacted]	[redacted]

Footnotes: *indicates results are undiscounted; deterministic results are presented in brackets.
Abbreviations: ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol-5 Dimension; Incr.: incremental; LYGs: life years gained; MF: myelofibrosis; PAS: patient access scheme; PV: polycythaemia vera; QALYs: quality-adjusted life years.

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Probabilistic (deterministic) results using the MF-8D are presented below in Table 4.

Table 4: Probabilistic (deterministic) results for the additional scenarios using the MF-8D (using the currently agreed PAS discount for MF)

Technologies	Total costs (£)	Total LYG*	Total QALYs	Incr. costs (£)	Incr. LYG*	Incr. QALYs	ICER (£/QALY)
Conservative case							
Current clinical management	£91,599 (£91,033)	8.13 (8.18)	6.17 (6.22)				
Ruxolitinib	[redacted]	8.53 (8.61)	[redacted]	[redacted]	0.40 (0.43)	[redacted]	[redacted]
More realistic case (in-between)							
Current clinical management	£91,622 (£91,033)	8.13 (8.18)	6.17 (6.22)				
Ruxolitinib	[redacted]	9.12 (9.22)	[redacted]	[redacted]	0.99 (1.04)	[redacted]	[redacted]

Footnotes: *indicates results are undiscounted; deterministic results are presented in brackets.
Abbreviations: ICER: incremental cost-effectiveness ratio; Incr.: incremental; LYGs: life years gained; MD-8D: Myelofibrosis 8 dimensions; MF: myelofibrosis; PAS: patient access scheme; PV: polycythaemia vera; QALYs: quality-adjusted life years.

Insert extra rows as needed

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

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

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References

1. National Institute for Health and Care Excellence (NICE), *Ruxolitinib for treating polycythaemia vera [ID5106]: Draft guidance consultation. Available at: https://www.nice.org.uk/guidance/GID-TA11079/documents/draft-guidance [Last accessed 20 June 2023].* 2023.
2. Alvarez-Larrán A, G.M., Ferrer-Marín F, Pérez-Encinas M, Mata-Vazquez MI, Bellosillo B, Arellano-Rodrigo E, Gómez M, García R, García-Gutiérrez V, Gasior M, Cuevas B, Angona A, Gómez-Casares MT, Martínez CM, Magro E, Ayala R, Del Orbe-Barreto R, Pérez-López R, Fox ML, Raya JM, Guerrero L, García-Hernández C, Caballero G, Murillo I, Xicoy B, Ramírez MJ, Carreño-Tarragona G, Hernández-Boluda JC, Pereira A; MPN Spanish Group (Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas),, *Real-world analysis of main clinical outcomes in patients with polycythemia vera treated with ruxolitinib or best available therapy after developing resistance/intolerance to hydroxyurea.* Cancer., 2022, 128 (13, 2441-2448
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Ruxolitinib for treating polycythaemia vera (review of TA356) [ID5106]

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Consultation on the draft guidance document – deadline for comments 5pm on 23 June 2023. Please submit via NICE Docs.

Appendix: Targeted search

Search strategy

Table 5: Embase and Medline search strategy using Embase.com (Searched on 24 May 2023)

#	Search terms	Facet	Hits
#1	'polycythemia vera'/exp		13,505
#2	'polycyth?emia' OR 'p vera' OR 'pv' OR 'pcv' OR 'pcrv' OR 'polycyth*' OR 'vaquez disease' OR 'cryptogenic polycythaemia' OR 'cryptogenic polycythemia' OR 'disease, vaquez' OR 'disease, vaquez osler' OR 'erythraemia' OR 'erythraemic myelosis' OR 'erythremia' OR 'erythremic myelosis' OR 'erythrocytemia' OR 'erythrocythaemia' OR 'erythrocythemia, cryptogenic' OR 'erythrocythemia, myelopathic' OR 'erythrocythemia, splenomegalic' OR 'erythrocytosis megalosplenica' OR 'morbus vaquez' OR 'myelopathic polycythaemia' OR 'myelopathic polycythemia' OR 'osler disease' OR 'osler vaquez disease' OR 'polycytemia vera' OR 'polycythaemia rubra vera' OR 'polycythaemia vera' OR 'polycythaemia vera benzene' OR 'polycythaemia, cryptogenic' OR 'polycythaemia, myelopathic' OR 'polycythemia rubra vera' OR 'polycythemia vera' OR 'polycythemia vera benzene' OR 'polycythemia, cryptogenic' OR 'polycythemia, myelopathic' OR 'primary polycythaemia' OR 'primary polycythemia' OR 'splenomegalic polycythaemia' OR 'splenomegalic polycythemia' OR 'vaquez osler disease'	Disease	84.503
#3	#1 OR #2		84.503
#4	'hydroxyurea'	PV AND HU AND survival	33,152
#5	'survival'		2,137,099
#6	**#3 AND #4 AND #5**		**594**
#7	**#3 AND #4 AND #5 AND [humans]/lim AND [english]/lim**		**556**

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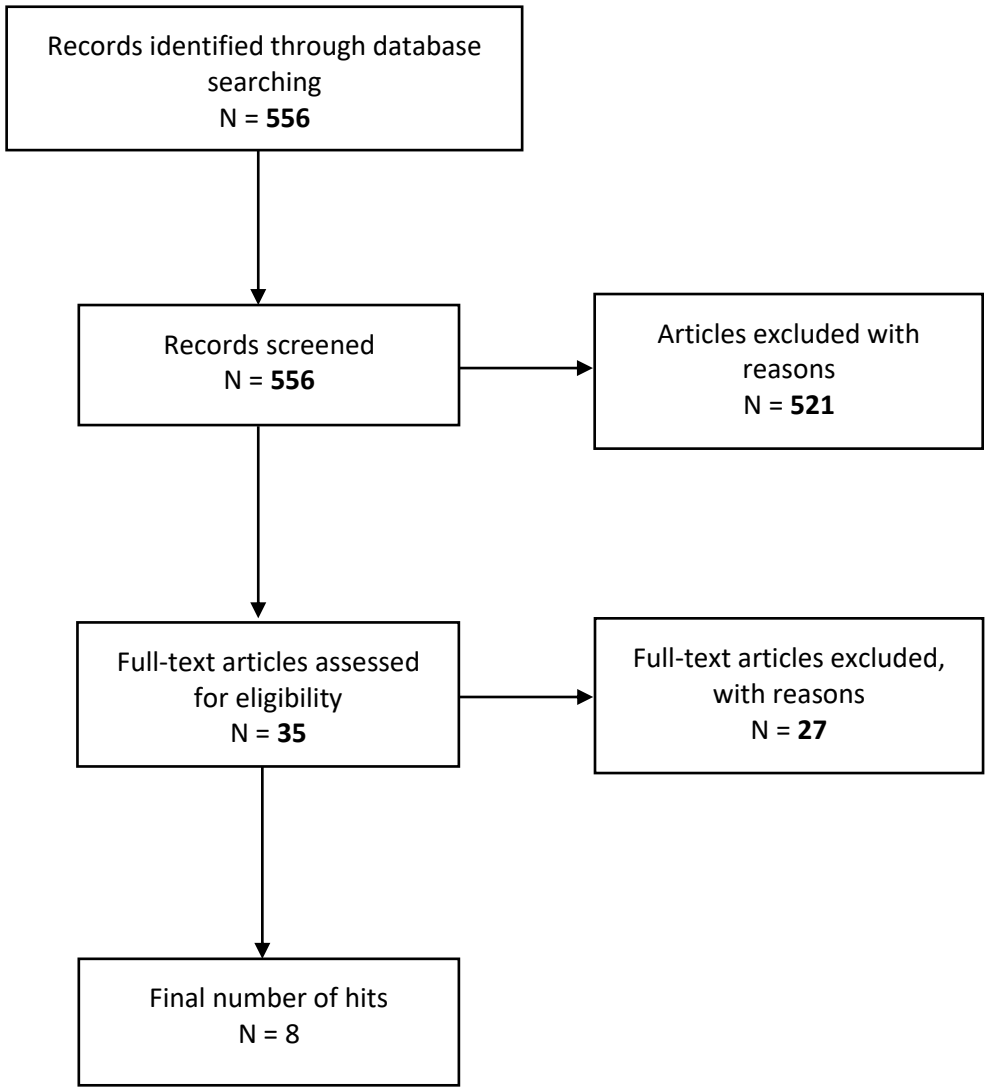
Prisma



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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	MPN Voice

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that the uncertainty in overall survival outcomes could prevent polycythaemia vera (PV) patients with a high unmet need from access to potentially life-changing treatment. The committee acknowledges the psychological impact of living with a rare condition. However, because PV is a rare condition, it is not possible for large enough trials to be conducted to investigate overall survival with certainty. As such, NICE's draft conclusion not to approve ruxolitinib presents a possible inequality issue for those with rare and less common conditions. Furthermore, the uncertainty means that the treatment could still improve overall survival for patients and given the high unmet need in this indication, we believe these patients deserve to have access to this treatment that could have a significant impact on both quality of life and overall survival.
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Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care and MPN Voice

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Leukaemia Care - [redacted], MPN Voice – [redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the uncertainty in overall survival outcomes could prevent polycythaemia vera (PV) patients with a high unmet need from access to a potentially life-changing treatment. The committee acknowledges the psychological impact of living with a rare condition. However, because PV is a rare condition, it is not possible for large enough trials to be conducted to investigate overall survival with certainty, for this appraisal or indeed any for the same condition. Without a rarity modifier in place, the NICE process is not fit for purpose for the review of drugs for groups that don't qualify as rare enough for HST, but also are disadvantaged in the standard NICE HTA process. As such NICE's draft conclusion not to approve ruxolitinib presents a possible inequality issue for those with rare and less common conditions. Furthermore, the uncertainty in the data doesn't necessarily mean that ruxolitinib doesn't improve overall survival for patients

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	and given the high unmet need in this indication, we believe these patients deserve to have access to this treatment, which could have a significant impact on both quality of life and overall survival.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	I have provided consulting services on two advisory boards to Novartis around the treatment landscape for hydroxycarbamide-resistant or intolerant polycythaemia vera (total value ~£1500). I have made no contribution to their NICE submission for the current STA.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Tim Somervaille

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Major comments** I would like to thank the committee for the opportunity to respond to the Draft Guidance on “Ruxolitinib for treating polycythemia vera.” I was pleased to note that the committee accepted that there is an unmet need for additional therapies in hydroxycarbamide-intolerant polycythemia vera (section 3.1). I was also happy to note that the committee accepted that there was strong evidence for the activity of ruxolitinib in hydroxycarbamide-intolerant polycythemia vera based on clinical trial data from RESPONSE and RESPONSE2 (section 3.4) and MAJIC-PV (section 3.6). In particular, MAGIC-PV shows significantly improved event-free survival for ruxolitinib versus best available therapy. While none of the clinical trials show a statistically significant improved overall survival I would comment that this is a particularly high bar to meet in polycythemia vera given the long baseline survival of patients with the disease.

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	I think an important point to make once more - and of course this point was made in committee and referred to in the Draft Guidance document - is that prolongation of overall survival with ruxolitinib versus best available therapy is entirely plausible. In MAGIC-PV there was a significant reduction in thromboembolic events and a trend towards a reduction in transformation events for ruxolitinib versus BAT. Both of these significant adverse outcome categories are associated with inferior survival in the longer term. Of course as a clinician treating patients with this disease I was deeply disappointed to see that the preliminary conclusion of the appraisal process was negative. I would reiterate to the committee that ruxolitinib is a safe and effective treatment which has transformed the lives of a number of my PV patients who had no other options for therapy. It is essential that this treatment is available on the National Health Service for the small number of patients who undoubtedly benefit from it. I would urge the committee to do whatever it can to facilitate conclusion of the current assessment process with a positive outcome. **One minor comment** is that towards the top of page 5 (lines 4-5) it is stated that an increase in white cells causes itching. This is not true. Patients with PV may suffer with intractable pruritus whether or not their white cell count is raised.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Claire Harrison, Guys and St Thomas' NHS Foundation Trust

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No funding from the tobacco industry
Name of commentator person completing form:	Claire Harrison

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	**Major comments** I am grateful for the opportunity to respond to the Draft Guidance on “Ruxolitinib for treating polycythemia vera.” I was glad to see that the committee accepted the unmet need for the relatively small proportion of polycythaemia vera (PV) patients failing hydroxycarbamide and acknowledged the demonstrated benefits of ruxoltinib in this setting as demonstrated in RESPONSE/RESPONSE 2 and MAJIC PV studies. I see the committee also recognised that as a solely UK trial comprised only of high risk PV patients failing hydroxycarbamide that this was a study reflecting the proposed indication. The size of this study given its very inclusive selection criteria and minimal exclusion criteria also suggest that numbers of patients requiring this therapy will be quite limited (NB 190 patients recruited in over 4 years) with many patients awaiting therapy so expecting numbers in real time to be smaller this was not particularly highlighted by the committee.

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	There was much discussion about the benefits beyond control of blood counts and improved quality of life. These are difficult to conclusively demonstrate as event rates are quite low with standard therapy and a very long study would be required and previous attempts to demonstrate this eg including matched pair analysis demonstrating reduction in thrombosis with ruxolitinib have limitations. However I wish to highlight once more to the committee that MAJIC -PV has demonstrated that ruxoltiinib provides superior EFS (thrombosis, haemorrhage, transformation and death). Furthermore in the subgroup of patients treated with ruxoltiinib whom had a molecular response – 50% reduction of driver mutation VAF that an overall survival advantage was obtained. Whilst measurement of molecular response is not standard practice this data does indicate a fundamental ability of this therapy to alter disease trajectory. For these reasons and that thrombosis is the predominant cause of death for PV patients (with a clearly statistically significant survival benefit for patients treated with ruxolitinib in MAJIC PV) I do fully anticipate that a survival benefit for patients treated with this therapy is entirely plausible. As a clinician treating patients with PV for over 20 years I recognise the impact of this disease upon quality of life and I was glad to note that the committee clearly recognised this and the very positive benefit of ruxolitinib upon important determinants of quality of life such as itch and fatigue. I am pleased to note that we shall have the chance to discuss this agent again in a follow up meeting and it is my fervent desire that the committee is minded to conclude positively regarding the benefits of this agent to patients who are otherwise faced with difficult choices such as for example taking a drug such as busulfan which might increase the risk of leukaemia several fold. Minor comment There is no relationship between itch and white cell count. Indeed we do not clearly understand the aetiology of itch in PV
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Insert extra rows as needed

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Evidence Assessment Group Report commissioned by the
NIHR Evidence Synthesis Programme on behalf of NICE

Ruxolitinib for treating polycythaemia vera (ID5106)

EAG critique of the company's response to draft guidance
and review of the progression-based model

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Joanne Lord Geoff Frampton
Correspondence to	Prof Joanne Lord Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	3 July 2023

1 Introduction

The Draft Guidance (DG) published for consultation on 2 June 2023 stated the committee's preferred assumptions for the cost-effectiveness modelling and requests for additional analyses. We summarise whether these issues were addressed in Table 1 and Table 2.

Table 1 Committee's preferred assumptions

Committee's preferred assumptions (DG 3.17)	Addressed in company response?
1. Best available therapy (BAT) as defined in the company submission was an appropriate comparator	No change required
2. MAJIC-PV was the most appropriate trial for decision making for the full marketing authorisation	Yes. MAJIC-PV used in committee-preferred analysis (see section 2.2 below) and other analysis in DG response.
3. The updated progression-based model structure was preferred in principle, although further validation of this structure, the evidence used to parametrise the model and its final outcomes was needed	Yes. Progression-based model used in DG response. Further validation provided by company (sections 2.3, 2.4, 2.5 below) and review by EAG (section 3 below).
4. EQ-5D was the most appropriate utility measure	Yes. EQ-5D used in committee-preferred analysis and scenarios. Results with MF-8D also reported.
5. Treatment waning was appropriate, as per the company's and EAG's bases cases as a conservative assumption. But it may not be appropriate in the updated progression-based model.	Waning is not applied in the revised model structure, as this does not use a HR to estimate the effect on overall survival.
6. A preferred extrapolation distribution for time to treatment discontinuation could not be determined, This was because would likely be affected by requests to change the model structure	Time to treatment discontinuation is modelled with a HR relative to time to progression (see EAG review section 3.3.3 below).

Table 2 Committee requests for additional analysis

Additional analyses (DG 3.18)	Addressed in company response?
1. Probabilistic sensitivity analyses results exploring the estimated hazard ratio for overall survival (DG section 3.13)	Yes. Effect explored in previous model structure (see section 2.6 below) and additional scenarios for updated model (section 2.7 below).
2. Scenario analyses results presenting more conservative assumptions for survival gain, including	Yes (see section 2.6 below).

an overall survival hazard ratio equal to 1 in the original model structure (DG section 3.13)	
3. A review of the appropriateness of the inputs and assumptions used in the updated progression-based model structure by the EAG	Yes (EAG review in section 3 below)
4. Probabilistic results for the updated progression-based model with committee preferred assumptions	Yes (see section 2.2 below).
5. Full independent clinical assessment to assess plausibility of the results	Additional Advisory Board conducted by company but limited detail reported (see section 2.3 below).
6. Validation of the model results for the relative effects on overall survival compared to MAJIC-PV results and longer-term registry data.	Yes. Comparison of model results against MAJIC-PV (section 2.4 below) and Alvarez-Larrán et al. 2022 registry (section 2.5 below)

2 EAG critique of the company's response to draft guidance

2.1 General comments

The company state that all analyses reported in their DG response were conducted using data from the MAJIC-PV trial and the progression-based model structure (with the exception of the scenario with no treatment effect on overall survival [OS], as requested by the committee). The results are all reported probabilistically, with EQ-5D utilities (in addition to MF-8D as scenarios). Results are reported with the current PAS discount agreed for the MF indication in TA386, [redacted].

2.2 Base-case probabilistic results using committee preferred assumptions

Results for the NICE committee's preferred base case are reported in Table 1 of the company's DG response. The EAG have replicated these results using the company's submitted model and confirm that they are consistent with the results from the previous version of the company's base case at Technical Engagement. See Table 8 (section 4 below) for the cumulative effect of introducing the committee's preferred assumptions.

2.3 Full independent clinical assessment of the plausibility of model results and inputs used for the progression-based model

The company sought expert opinion on the clinical plausibility of the model inputs and results at a virtual Advisory Board (13th June 2023) attended by 10 clinical experts. Five of the experts had validated the original CS and the other five were identified based on

recommendations of the original experts. The pre-meeting reading material [1] and an agenda and meeting summary [2] were provided by the company. The experts' opinions relating to specific data sources and assumptions are listed in the meeting summary. The experts agreed with the company's choice of data sources for the change in transformation risk through time (Szuber et al. 2019 [3]), expected survival following AML/MDS (Tang et al. 2017 [4]) and long-term OS (Alvarez-Larrán et al. 2022 [5]) and were not aware of any better alternative sources for these data. The company conducted a targeted search for alternative real-world sources of OS data which we critique in section 2.5 below.

The 10 experts were from Oxford (3 experts), London (2 experts), Birmingham, Cambridge, Glasgow, Manchester and Newcastle (1 expert each), which gives a broad UK coverage of NHS practice. The company do not comment on the details of each expert's centre/institution, such as their specialisms, patient catchment areas and numbers of patients seen annually. However, given the number of centres included it seems likely that the centres are broadly representative of those which manage patients with PV in the NHS.

Six of the 10 experts were authors on the MAJIC-PV trial paper and two of the experts had advised the first NICE Advisory Committee Meeting for this topic. No potential conflicts are listed in the company's response so it is not fully clear to what extent the experts may have other potential conflicts.

The company's summary of the outcome of the expert consultation is very general, mentioning that there was a "consensus" of opinion but without indicating how many experts agreed or disagreed with each of the issues discussed, nor mentioning whether those who agreed or disagreed were those with potential conflicts or whether any experts abstained from giving answers. It is therefore not clear how uncertain the outputs from the clinical validation exercise are. The company concluded that "clinical experts considered the model predictions under the base case more likely to be plausible than not but highlighted the uncertainty".

In summary, the EAG do not believe that the expert consultation exercise has reduced the uncertainty around the validity and plausibility of the model inputs, since insufficient information on the expert engagement process, and in particular the variation in experts' responses, is reported. However, it appears likely that all relevant sources of data have been identified by the company since no experts were aware of any better alternatives.

2.4 Comparison of model predictions using the progression-based model against the MAJIC-PV results

Figures 1 and 2 in the company's DG response show model predictions for progression-free survival (PFS) and overall survival (OS) using the committee's preferred assumptions, compared with KM results from the MAJIC-PV trial. We confirm that these results accurately reflect the output of the submitted model. The predictions have a reasonable fit to the trial results, given the variation in the KM curves. We note that the MAJIC-PV trial was not powered for the PFS and OS outcomes, and that the numbers of deaths and incident cases of MF and AML/MDS were low (see section 3.3.1.1 below).

2.5 Validation of model results against external data

The company conducted a targeted literature search to identify studies that report survival of patients with PV who are resistant or intolerant to hydroxycarbamide. A targeted search is a pragmatic way to identify relevant evidence when time and resources are limited. The company state in their response that searches were conducted in Embase and Medline by "an independent reviewer" but provide relatively limited further information.

The EAG have the following concerns regarding the targeted search:

- The search strategy has no synonyms for hydroxyurea (e.g. the term "hydroxycarbamide" is not included).
- The search strategy does not specify which database fields were searched (i.e. title, abstract, keywords and/or others).
- The screening process appears to have been conducted by only one reviewer. Any errors or selective inclusions/exclusions would therefore not have been detected.
- Standard practice in evidence synthesis is to list the studies that were excluded at full-text screening with the reason(s) for exclusion. The PRISMA chart provided by the company states "Full text articles excluded, with reasons" but no list of the references excluded at full text screening is provided.
- The PRISMA chart does not explain whether "records" refers to titles and/or abstracts, and refers to "articles" and "hits" but not studies, so it is unclear how the number of articles screened links to the number of studies included/excluded.

Due to the limitations listed above, it is possible that the search may have missed relevant studies and it is unclear whether studies that were identified were appropriately excluded. The EAG conducted a rapid targeted search in Google Scholar using a basic search string ("polycyth[a]emia vera survival") to check for relevant studies published after 2021. We did

not identify any potentially relevant new studies for patients who were resistant or intolerant to hydroxycarbamide. And as noted in section 2.3 above, the company's expert Advisory Board were not aware of any better alternative sources of survival data. We therefore conclude that the Alvarez-Larrán et al. 2022 cohort [5] is likely to be the most relevant currently available source of long-term OS data for the cohort of interest.

2.6 Scenario requested by the committee assuming no difference in survival using the original model structure

This scenario was requested to explore the impact of uncertainty over the hazard ratio for overall survival from the MAJIC-PV trial, which has a wide confidence interval. The hazard ratio is not used in the progression-based model, hence the request to run the scenario in the original model. The company report the results in Table 2 of their DG response. As might be expected, the scenario causes a large increase in the ICER: from [redacted] per QALY gained with the committee's preferred assumptions, to [redacted] per QALY in the scenario (probabilistic results). The EAG replicated these results using the company's model.

2.7 Additional scenarios around the size of the treatment effect for overall survival using the progression-based model

The company report two additional scenarios to test the impact of assumptions about the survival benefit of ruxolitinib in the progression-based model: a 'conservative' scenario in which ruxolitinib only affects deaths though a reduction in the incidence MF and AML/MDS; and a 'more realistic' scenario in which ruxolitinib does reduce pre-progression mortality, but not by as much as in the base case. The latter scenario is implemented by estimating pre-progression survival for ruxolitinib by applying a hazard ratio to the pre-progression survival curve for the BAT arm. The impact of these two scenarios on the OS curves is illustrated in DG response Figure 4, and the cost-effective results are reported in Table 3. Both scenarios are still associated with a large increase in the ICER, compared with the base case. We replicated these scenario results using the company's model.

The EAG consider that the company's 'conservative' scenario provides a reasonable bound on the effect of uncertainty over the pre-progression survival benefit with ruxolitinib. The MAJIC-PV trial showed a significant reduction in thromboembolic events, and the 'conservative' scenario excludes an effect on deaths due to thromboses. However, we do also note that the company's base case model includes an adjustment of the observed incidence of AML in the MAJIC-PV trial, which was actually lower in the BAT arm than in the ruxolitinib arm (see section 3.3.1.1 below). We report results from a company scenario analysis using the observed AML incidence rate from MAJIC-PV trial (see Table 10 below).

3 EAG review of the assumptions and inputs in the progression-based model

3.1 Introduction

The models in the company's original submission for this appraisal used health states based on treatment rather than disease status (CS Figure 35).[6] The company submitted an alternative progression-based model with their response to Technical Engagement: key issue 5, and Appendix. [7 8] The company's illustration of the progression-based model structure is reproduced in Figure 1 below.

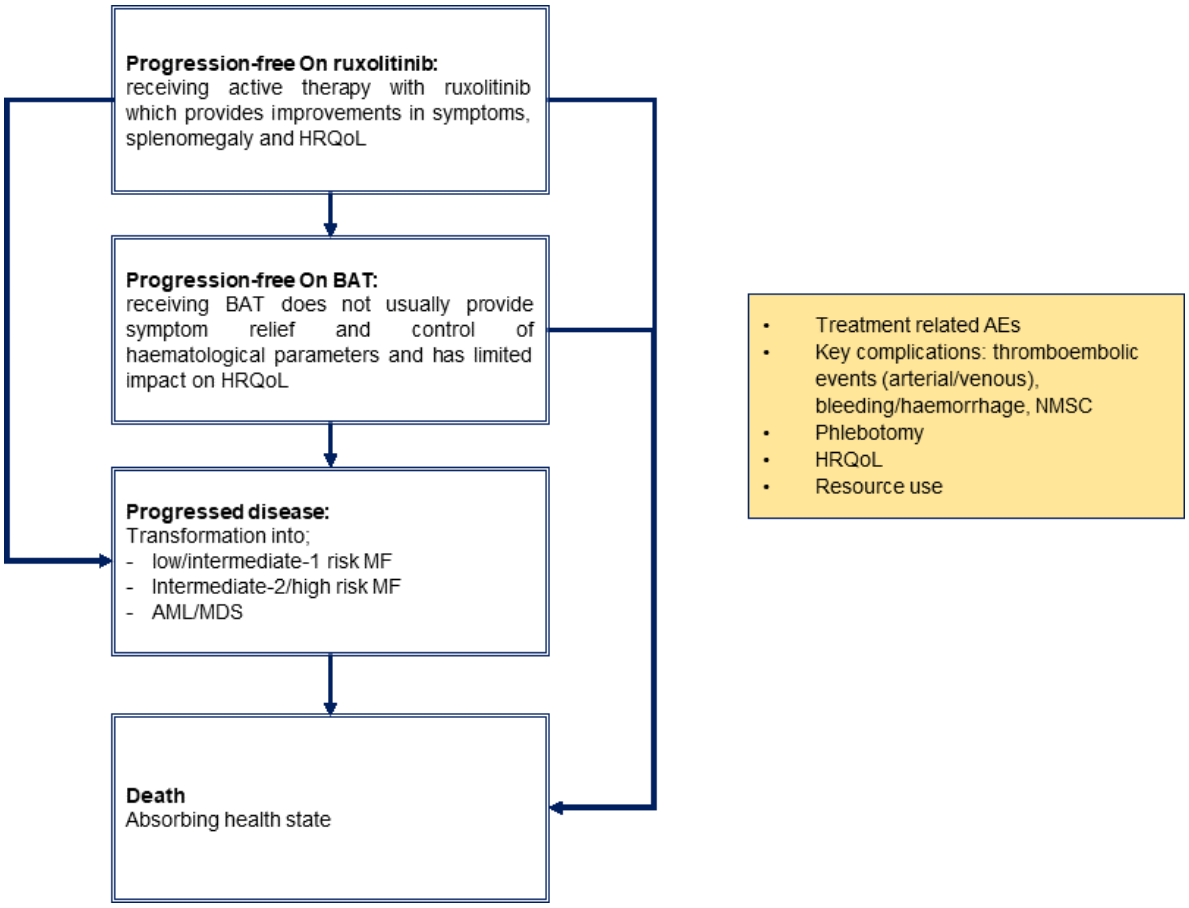

Figure 1 Illustration of the progression-based model structure

Abbreviations: AE: adverse event; AML: acute myeloid leukaemia; BAT: best available therapy; HRQoL: health-related quality of life; MDS: myelodysplastic syndrome; MF: myelofibrosis; NMSC: non-melanoma skin cancer.
Source: Reproduced from Figure 1 in the company's Technical Engagement response appendix [8]

The EAG consider that the progression-based model structure provides a better reflection of the disease process and is more likely to provide an accurate estimation of survival gain than the original model. We reported preliminary checks on the progression-based model in the EAG critique of the company's Technical Engagement response, concluding that the model was correctly implemented and that the results had face validity.[9] However, due to a

lack of time, we did not provide a critique of the assumptions and additional data sources in the model.

The Draft Guidance (DG) issued in May 2023 stated that the committee preferred the progression-based model structure in principle, but noted that this was subject to considerable uncertainty.[10] The NICE committee specified their preferred assumptions and requested additional analyses and further evidence to enable decision-making, including a review of the appropriateness of the inputs and assumptions in the progression-based model by the EAG. We report this review in the following sections. As the committee have specified that MAJIC-PV trial is the most appropriate basis for decision making, we focus on the MAJIC-PV version of the model.

3.2 Model structure and assumptions

3.2.1 Definition of progression

The model uses a definition of progression based on the progression-free survival (PFS) outcome in the MAJIC-PV trial: transformation to myelofibrosis (MF), myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML), or death from any cause.[11] The MAJIC-PV trial publication also reports event-free survival (EFS): a broader composite including transformation to MF, MDS or AML and major thrombosis, major haemorrhage, or death from any cause. The trial results showed a significant improvement with ruxolitinib for EFS (HR 0.58; 95% CI 0.35 to 0.94; p=0.03), but not for PFS (HR 0.64; 95% CI 0.36 to 1.15; p=0.13).[11]

The company state that it is not possible to construct a model based on EFS from the reported results from MAJIC-PV, as the numbers of thrombotic and haemorrhagic events have not been reported by treatment arm (Table S9 in the trial publication [11]). They also argue that a model based on EFS could only account for the first event within this composite outcome; and that it would be difficult to estimate the prognostic effect of thrombosis or haemorrhage on survival without additional data on the types of events and patient characteristics. It would be possible to overcome these limitations, but only by increasing the complexity of the model structure (e.g. by adding multiple health states for second and subsequent events, or moving to an individual-level simulation), which would require additional assumptions and input estimates.

There is a downside to modelling complications with lasting health impacts as events rather than as health states. In particular, the survival impact of thromboses and bleeds may not be

fully captured, suggesting that the survival benefit of ruxolitinib may be underestimated. The QALY losses assumed for thromboses and bleeds in the company's model include utility lost during expected survival with these complications, but not the QALY loss associated with the shortened life expectancy per se. In theory, survival extrapolations based on all-cause survival from the MAJIC-PV trial should incorporate deaths due to thromboses and bleeds, but the trial was not powered for these outcomes and the five-year follow up may be insufficient due to time lags between onset of the complications and related mortality.

Conversely, underestimating the long-term impact of non-melanoma skin cancer (NMSC), which is also modelled as an event, would tend to favour ruxolitinib. However, the long-term health impacts of NMSC are relatively low (the company assume no QALY loss for NMSC).

On balance, the EAG agree with the company's decision to base the model on progression defined as transformation to MF or AML/MDS. Attempting to model thromboses and bleeds as health states rather than events would likely add to uncertainty, rather than resolving it.

We also agree with the use of sub-states within the progressed disease state to differentiate by level of risk and management:

- Low/intermediate-1 risk MF (ruxolitinib not recommended for this subgroup in TA386)
- Intermediate-2/high risk MF (ruxolitinib recommended for this subgroup in TA386)
- Leukaemia, including AML and MDS.

These sub-states are modelled using tunnel states, and are associated with different survival extrapolations, treatment costs and utilities.

3.2.2 State transition modelling approach

The company use a state-transition modelling approach, rather than a partitioned-survival approach as in their original model for the MAJIC-PV population. In principle, we agree that, where the data is available to estimate transition probabilities, a state transition model is superior to a partitioned survival model. We discuss the robustness of the pre- and post-progression survival estimates used to model transitions in sections 3.3.1 and 3.3.2 below.

3.2.3 No partition by BAT line of treatment in progressed state

In this alternative model structure, the company did not implement a partitioning of the BAT health state. This is in line with the EAG preferred assumption, based on clinical opinion that there is not a clear treatment pathway for this condition.

3.3 Input parameters

3.3.1 Progression-free survival

Time spent in the progression-free health states ('On ruxolitinib' and 'On BAT') is governed by three sets of survival curves:

- Pre-progression survival (PrePS): reflecting 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

Methods for estimating these survival curves are described in section 1.2.1 of the appendix to the company's Technical Engagement response. In each case, an extrapolation based on an observed Kaplan-Meier (KM) survival curve is used to model how the hazard for the event changes over time, then adjusted to fit an estimated 5-year probability of the event.

3.3.1.1 Adjustment of PrePS, MFS and LFS for 5-year trial probabilities

The company's estimates of the 5-year probabilities are shown in Table 3 below. There was only one case of MDS and no AML observed in the MAJIC-PV BAT arm over 5 years.[11] The company argue that this is inconsistent with published literature (Alvarez-Larrán et al. 2022)[5] and that clinical experts have advised that this is likely due to chance, given the small sample size. The company therefore used an alternative estimate of the BAT 5-year probability of AML/MDS in their base case model: 5.69% based on the ratio of MF to AML/MDS reported in the Alvarez-Larrán et al. 2022 Spanish cohort study (14.49% * 11/28). The model includes an option to use the observed probability of AML/MDS (1.67%), which we report as an EAG scenario (see Table 10).

Table 3 Estimated 5-year probability of transitions from progression-free health states

Arm	N	Number of events at 5 years in the MAJIC-PV trial			Probability at 5 years, excluding competing events		
		MF [a]	AML/MDS [a]	Death [b]	MF	AML/MDS	Death [b]
Ruxolitinib	93	5	4	12 [c]	6.49%	5.26%	14.29%
BAT	87	10	1	17 [c]	14.49%	1.67% (5.69%) [d]	22.37%

Source: Adapted by the EAG from Appendix Table 1 in the company's Technical Engagement response

[a] From MAJIC-PV trial publication (Harrison et al. 2023) Supplementary Appendix Table S11B;[11]

[b] Death prior to transformation;

[c] Estimated from MAJIC-PV PFS KM data;

[d] Estimate used in the model from the probability of MF (14.49%) multiplied by the ratio of MF to AML/MDS in the Alvarez-Larrán et al. 2022 study (39.29%, 11/28).[5]

3.3.1.2 Pre-progression survival (PrePS)

The change in the hazard for mortality prior to transformation to MF or AML/MDS over time was estimated by fitting survival distributions to the reported KM curve for PFS in MAJIC-PV (trial publication[11] supplementary appendix Figure S4C). The company used a Weibull distribution for both ruxolitinib and BAT PrePS in their base case. The KM and Weibull PFS extrapolations are shown in Figure 3 of the appendix to the company's Technical Engagement response.

The company state that their choice of the Weibull distribution was based on visual fit, statistical fit and plausibility, but further explanation and statistics are not provided in their consultation response. However, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) model fit statistics are included within a model spreadsheet. Table 4 and Table 5 below show the AIC/BIC statistics and survival predictions, respectively, for the distributions with the best statistical fit.

Figure 2 and

Figure 3 also illustrate these extrapolations. The exponential, lognormal and loglogistic curves all have a slightly better statistical fit than the Weibull, although the absolute AIC and BIC statistics are very similar for these four functions. The Gompertz AIC and BIC statistics are also similar, but slightly worse than those for the Weibull.

The company presented scenario analyses for alternative PrePS distributions in Figure 10 of the appendix to their Technical Engagement response. This showed that the model was sensitive to the choice of distribution. We report scenario analysis for the PrePS distributions in Table 10 below.

Table 4 Statistical fit of extrapolations fitted to MAJIC-PV PFS KM

Survival distribution	BAT				Ruxolitinib			
	AIC	BIC	Rank AIC	Rank BIC	AIC	BIC	Rank AIC	Rank BIC
Exponential	[redacted]							
Weibull	[redacted]							
Lognormal	[redacted]							
Loglogistic	[redacted]							
Gompertz	[redacted]							
Hazard spline1	[redacted]							
Odds spline1	[redacted]							
Normal spline1	[redacted]							

Source: Produced by the EAG from data reported in the company's DG response model

Table 5 Predicted PFS of extrapolations fitted to MAJIC-PV PFS KM data

Survival distribution	BAT: prediction at year					Ruxolitinib: prediction at year				
	5	10	15	20	25	5	10	15	20	25
KM data	[redacted]					[redacted]				
Exponential	[redacted]					[redacted]				
Weibull	[redacted]					[redacted]				
Lognormal	[redacted]					[redacted]				
Loglogistic	[redacted]					[redacted]				
Gompertz	[redacted]					[redacted]				
Hazard spline1	[redacted]					[redacted]				
Odds spline1	[redacted]					[redacted]				
Normal spline1	[redacted]					[redacted]				

Source: Produced by the EAG from data reported in the company's DG response model

Figure 2 PFS extrapolations for the MAJIC-PV trial BAT arm

Source: reproduced by the EAG from the company's model

Figure 3 PFS extrapolations for the MAJIC-PV trial ruxolitinib arm

Source: reproduced by the EAG from the company's model

3.3.1.3 Time to transformation (MFS and LFS)

Data from a cohort of 665 patients with PV who were referred to the Mayo clinic (Szuber et al. 2019) were used to estimate how the hazard for transformation to MF and AML/MDS changes over time.[3] The Mayo PV cohort was not restricted to patients with resistance or intolerance to hydroxycarbamide and 91% were referred within one year of diagnosis, so they differ from the population of interest in this appraisal and the MAJIC-PV population (mean time since diagnosis 91 months, Harrison et al. 2023 Table 1).[11] The company note this difference and adjust for it by using the Mayo clinic data from 92 months onwards.

The company fitted Weibull distributions to the MFS and LFS KM curves reported for the Mayo cohort (Figure 1B and 1C in Szuber et al. 2019).[3] The company did not provide any justification for their choice of Weibull extrapolations, and alternative distributions were not reported or included in the model. However, the visual fit of the extrapolations to the KM data appears reasonable: see Figure 4 below (reproduced from Figure 2 in the appendix to the company's response to Technical Engagement).

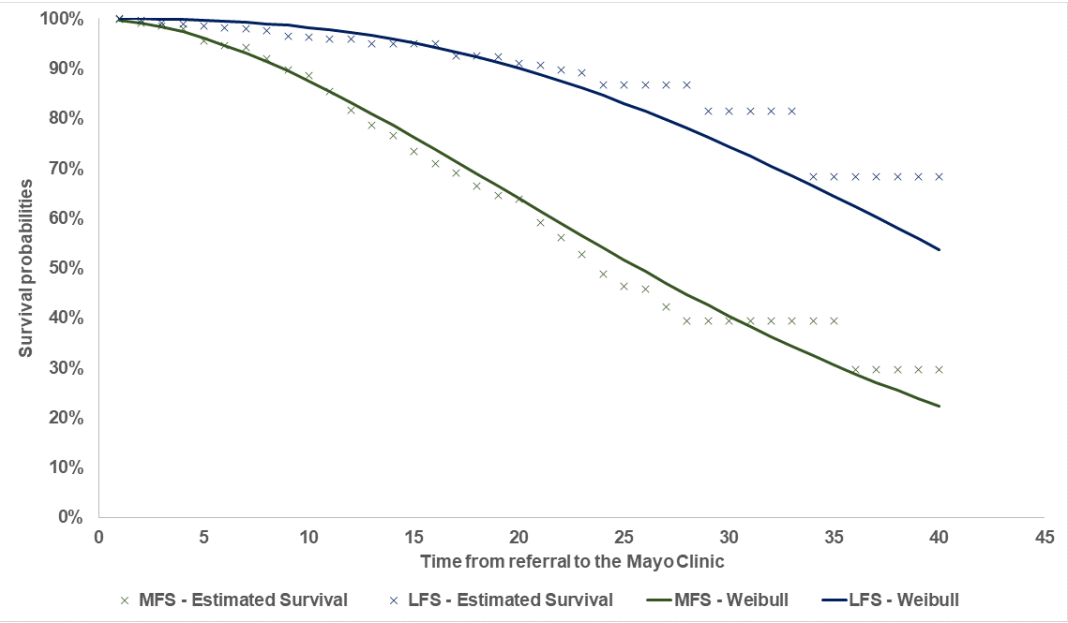

Figure 4 MFS and LFS in the Mayo cohort and a fitted Weibull distribution

Source: reproduced from Figure 2 in the Company Technical Engagement response appendix

The MFS and LFS curves were adjusted for the ruxolitinib and BAT arms using 5-year probabilities for these two types of event (see Table 3 in the following section). For the company's base case, the adjusted MFS and LFS curves were both more favourable for ruxolitinib than for BAT (Figure 6). The base case LFS curve relies on the company's estimate for the 5-year probability of AML/MDS in the BAT arm (5.69%) based on the ratio of

MF to AML/MDS from Alvarez-Larrán et al. 2022.[5] Using the lower 5-year probability of AML estimated directly from MAJIC-PV data (1.67%) results in a much more favourable LFS curve for BAT (see Figure 5 and Figure 6 below).

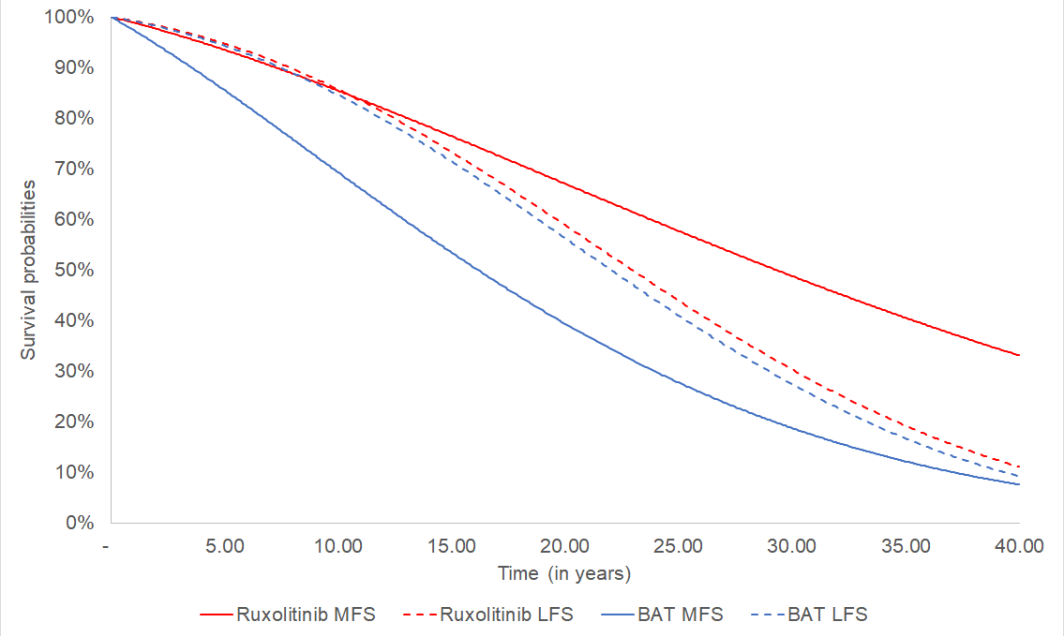

Figure 5 Base case MFS and LFS extrapolations for ruxolitinib and BAT

Source: Produced by the EAG from the company's model
5-year probability of AML/MDS for BAT (5.69%);

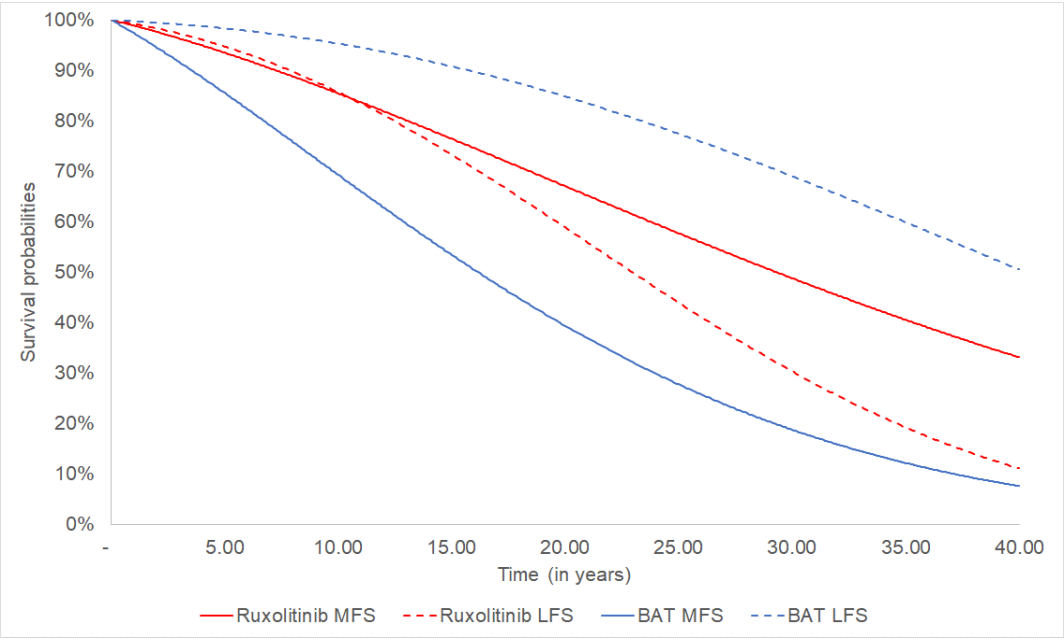

Figure 6 MFS and LFS extrapolations for ruxolitinib and BAT

Source: Produced by the EAG from the company's model
Scenario with 5-year probability of AML/MDS estimated directly from MAJIC-PV (1.67%)

3.3.2 Post-progression survival

OS extrapolations following transformation to MF or AML/MDS are described in section 1.2.2 of the appendix to the company's Technical Engagement response:

- **AML**: A Weibull distribution was fitted to survival data for a small US cohort of PV patients in the accelerated/blast phase (n=39, 30 events) (Figure 1 in Tang et al. 2017).[4] The company do not justify the selection of this source.
- **Low/intermediate-1 risk MF**: The source for the OS estimates in this subgroup is not clearly stated. The description in the company Technical Engagement response appendix states that Tefferi et al. 2019 is the source for the KM data, however the reference provided is to a 2012 paper by Tefferi et al.[12] The model includes a Weibull curve fitted to KM data for the intermediate-1 risk group. This curve is then adjusted for the low risk group using a hazard ratio derived from a 2009 paper by Cervantes et al.[13]
- **Intermediate-2/high-risk MF**: OS estimates are taken directly from the Novartis model for TA386, with an assumption that 23% of patients in this group would receive ruxolitinib (Mead et al. 2022)[14 15]

Figure 7 Survival following transformation to MF or AML/MDS

Source: Reproduced from Figure 4 in the appendix to the company's Technical Engagement response

3.3.3 Time to treatment discontinuation (TTD)

The company modelled time on treatment relative to PFS, using a hazard ratio for TTD compared with PFS (1.055; 95% CI: 0.59 to 1.90) estimated from pseudo individual patient data generated from the MAJIC-PV KM curves for TTD and PFS (Figure 8). This approach preserves the close correlation between discontinuation of ruxolitinib and transformation to MF, MDS or AML. This correlation is not surprising because the MAJIC-PV trial protocol specified that treatment with ruxolitinib should stop on progression to MF, MDS or AML. The company states that clinical advisors have confirmed that this would apply in practice, except for patients who would continue treatment for MF. The EAG agrees that this approach to modelling TTD is appropriate, given that uncertainty over the hazard ratio is integrated in the company's probabilistic sensitivity analysis.

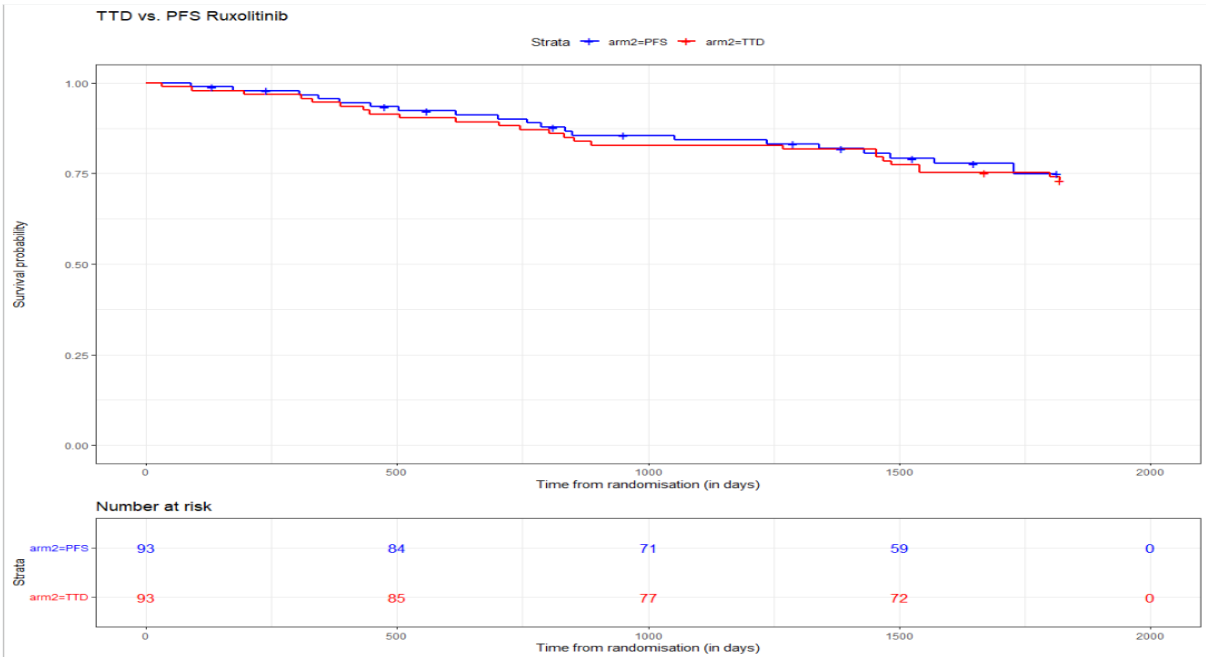

Figure 8 Comparison of the KM for TTD and OS in MAJIC-PV

Source: reproduced from company TE response appendix Figure 7

3.3.4 Incidence of other complications

The incidence of thrombosis, bleeding and non-melanoma skin cancer (NMSC) are the same as in the original model (CS Tables 24 and 25), except for the addition of a multiplier to adjust for increasing incidence of venous thromboembolism with age from a Danish national cohort (Arnesen et al. 2022).[16] This multiplier is used in the company's base case and applied to both thrombosis and bleeding events. Removing the multiplier has a very small impact on the ICER.

3.3.5 Health-related quality of life

Table 2 in the company's technical engagement response appendix sets out the utility values used in their previous base case model. We summarise the utility values in the DG response analysis with committee preferred assumptions in Table 6 below. Where possible we have checked that these values are consistent with the cited references, although we do not have access to confidential data from TA386. The utilities in Table 6 have been applied appropriately in the model.

Table 6 Utility inputs to model

Health state	Parameter	Value in model	Source
Progression-free on ruxolitinib	Utility	[redacted]	Response-2 EQ-5D-5L mapped to 3L (CS B.3.4.1)
Progression-free on BAT	Utility	[redacted]	
AML/MDS	Disutility	-0.13	Difference between AML utility (0.74, Mamolo et al. 2019 [17]) and US population norm (0.87)
MF low / intermediate-1	Disutility	[redacted]	Difference between MF utility (0.71, Mesa et al. 2021 [18]) and baseline EQ-5D in RESPONSE-2 ([redacted])
	QALY loss	[redacted]	Additional QALY loss (discounted) during supportive care, applied at transformation. Estimated as in TA386: utility loss -0.023 every 24 weeks for mean duration of [redacted] weeks.
MF intermediate-2 / high	QALYs	[redacted]	Total lifetime QALYs (discounted) as in TA386. Weighted sum for patients on ruxolitinib ([redacted]) and usual care ([redacted]). 23% on ruxolitinib (Mead et al. 2022 [14])

3.3.6 Cost and resource use for MF and AML

Costs for management of transformation events are reported in the technical engagement response appendix (section 1.2.5). We summarise the costs applied in the DG response analysis in Table 7 below and confirm that these values reflect the cited sources (except for those based on confidential data in TA386) and have been applied correctly in the model.

Table 7 Cost inputs to model

Health state	Parameter	Value in model	Source
AML/MDS	Cost per 28-day cycle	£2,657	£2,520 per month (Wang et al. 2014[19] Table 6), adjusted for 28-day cycle and 2021 prices
MF low / intermediate-1	Cost per 28-day cycle	£298	NHS costs for management, see TE response appendix Table 3
	Supportive care	[redacted]	Approximately £55 per week for [redacted] weeks.
	End of life care	£18,400	Assumes one outpatient visit and two red blood cell units for 18 weeks
MF intermediate-2 / high	Total cost per transformation	[redacted]	Weighted discounted cost from TA386, assuming 23% have ruxolitinib ([redacted]) and 77% usual care ([redacted]). Uplift to 2021 prices applied to non-drug costs only ([redacted] for ruxolitinib and [redacted] for BAT costs)

4 Cost effectiveness results

Table 8 shows how the cost-effectiveness results change as the committee's preferred assumptions are added, one at a time, to the company's previous base case for the MAJIC-PV population. For this population, the change from the previous model structure to the progression-based model causes a small decrease in the ICER. The change from MF-8D to EQ-5D based utilities causes a large increase. In addition to the committee's preferences, the company included a small correction to the cost of thrombosis previously recommended by the EAG. This had a negligible impact on the ICER. These and other results in this report are conducted with the current PAS discount for ruxolitinib.

Table 8 Cumulative impact of committee-preferred assumptions (deterministic)

Assumption	Treatment	Total		Incremental		ICER
		Cost	QALYs	Cost	QALYs	
Company's MAJIC-PV base case post TE	BAT	£83,317	6.11			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ EAG thrombosis cost	BAT	£83,339	6.11			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Progression-based model structure	BAT	£91,033	6.22			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ EQ-5D utilities	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Committee preferred	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: EAG analysis using the company's model.

We report the deterministic results here because the probabilistic sensitivity analysis (PSA) is very slow to run. The deterministic results are also stable, whereas the probabilistic results vary when PSA is re-run.

The company report probabilistic results with the committee's preferred assumptions, with 2,000 iterations (Table 9). The results are similar to the deterministic results. The EAG re-ran the company's probabilistic analysis and found similar results.

We show deterministic results with selected scenarios in Table 10.

Table 9 Cost-effectiveness results with the committee's preferred assumptions

Assumption	Treatment	Total		Incremental		ICER
		Cost	QALYs	Cost	QALYs	
Deterministic analysis	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic analysis	BAT	£91,511	5.82			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: EAG analysis using the company's model.						

Table 10 Selected scenario analyses (deterministic)

Assumption	Treatment	Total		Incremental		ICER
		Cost	QALYs	Cost	QALYs	
Committee preferred	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original model	BAT	£83,339	5.71			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS effect: HR=1 original model structure	BAT	£83,339	5.71			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS effect: company's 'conservative' scenario	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS effect: company's 'in-between' scenario	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAT AML 5-year probability 1.67%	BAT	£91,406	6.22			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression survival: exponential	BAT	£95,517	6.12			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression survival: lognormal	BAT	£97,308	6.23			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression survival: loglogistic	BAT	£96,129	6.16			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression survival: Gompertz	BAT	£84,666	5.54			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR TTD versus PFS: lower limit (0.59)	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR TTD versus PFS: upper limit (1.90)	BAT	£91,033	5.88			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility; MF-8D	BAT	£91,033	6.22			
	Ruxolitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: EAG analysis using the company's model.						

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