Ruxolitinib for treating polycythaemia vera

For public – AIC and CIC information redacted [redacted]

Corrections made to slides 29 and 30 post ACM1

Technology appraisal committee D [11 May 2023]

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Company: Novartis Pharmaceuticals

Background on polycythaemia vera

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

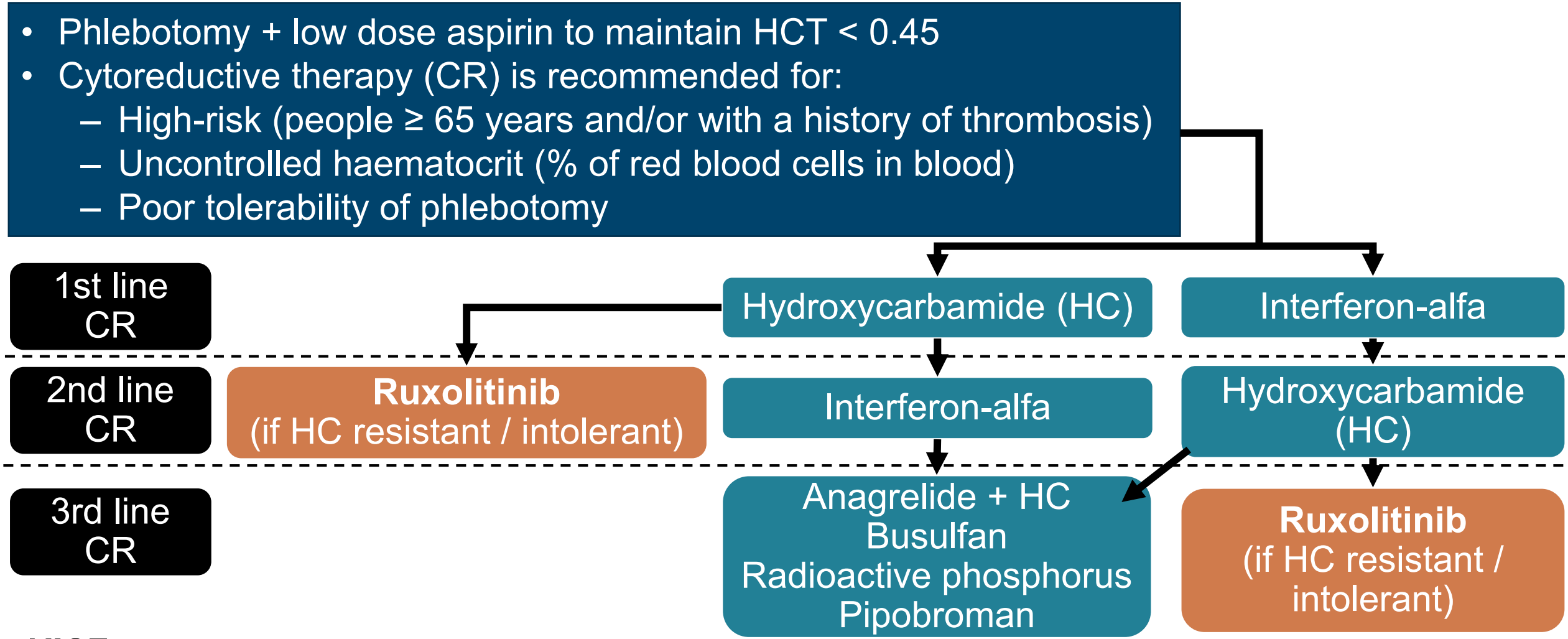
- Diagnosis via blood test to check red blood cell count or haematocrit level
- Symptoms include headaches, blurred vision, red and/or itchy skin, tiredness, high blood pressure, dizziness, confusion, bleeding problems, and gout
- Lower life expectancy due to increased risk of blood clots, an enlarged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

Abbreviations: JAK2, janus kinase 2; PV polycythaemia vera

Treatment pathway

Ruxolitinib could be given to people who are intolerant to hydroxycarbamide

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



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

Patient perspectives (1)

Submission from MPN Voice & Leukaemia Care

Unmet need

- PV can be an extremely debilitating illness that affects people with PV as well as their families and carers
- ~ 25% of people report becoming intolerant to first-line treatments due to side effects or declining treatment effectiveness
- Current treatments do not adequately reduce fatigue, bone pain or pruritis (itching), people also need frequent venesections which are highly disruptive

"The disease has greatly affected my quality of life…I can be good one day but the next day I'm in so much pain I have to rest…I have booked holidays, flights, etc. and lost money because I've ended up in hospital"

"I was then prescribed hydroxycarbamide…my bloods again became difficult to control, I still had itching, fibre in my marrow, rosacea and my spleen enlarged again…but worst of all my fatigue increased…it was severely impacting on my work"

Abbreviations: MPN, myeloproliferative neoplasm

Patient perspectives (2)

Submission from MPN Voice & Leukaemia Care

Benefits of ruxolitinib

- Ruxolitinib is an additional treatment option for people where long term use of hydroxycarbamide carries an unacceptable risk of developing other cancers
- Improved control of blood counts and significantly improved symptoms including reduced fatigue, spleen size, pain and itchy skin
- The following potential risks associated with ruxolitinib can and should be mitigated so benefits outweigh risks:
  - Increased infections
  - Skin cancer
  - Weight gain, blood pressure, cholesterol

"I was prescribed ruxolitinib. There were some side effects at first but since then, I have had no migraines, my blood counts are finally back in normal range, I have no itching and my spleen has shrunk"

"The improvement in my condition was immediate and transformational, dramatically so I would say! All previous symptoms subsided, no more itching, rosacea, my spleen went back to practically normal and I got my life back"

NICE

Abbreviations: MPN, myeloproliferative neoplasm

Clinical perspectives

Technical engagement responses from clinical experts

Unmet need

- Ruxolitinib would open up another treatment option and have a significant impact on quality of life
- Current treatment options, such as busulfan, increase the risk of leukaemia which may be fatal within 3 to 6 months

Benefits of ruxolitinib

- Ruxolitinib assists in maintaining the haematocrit at <45% and reduces the requirement for hospital based venesections*
- Improved symptom burden (i.e., night sweats, itching, fatigue)
- Ruxolitinib already in widespread used to treat myelofibrosis

"A small daily dose of ruxolitinib can be sufficient to completely abolish the severe…itching of the skin that some PV patients can experience which can be so bad that patients are unable to shower or bathe in view of the skin pain it induces"

*A venesection (or phlebotomy) involves removing blood from a person to reduce excess red blood cells

Abbreviations: PV, polycythaemia vera

Equality considerations

Equality considerations

- No equality issues were identified

Key issues

Table: Key issues not resolved during technical engagement for discussion

Key issues	ICER impact
Generalisability: Which of the 3 ruxolitinib trials should be used for decision-making?	Large
Company's model: Is the company's original model appropriate for decision making?	Large
Estimating treatment effect: What assumptions should be made for OS treatment effect in the model?	Large
Utility estimates: Is EQ-5D or MF-8D more appropriate?	Large
Treatment discontinuation: Is odds spline or Weibull extrapolation for ruxolitinib TTD preferred?	Small

Abbreviations: NHS, National Health Service; OS, overall survival; TTD, time to discontinuation

Ruxolitinib (Jakavi, Novartis Pharmaceuticals)

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

Decision problem

	Final scope	Company	EAG
Population	Adults with PV that is resistant or intolerant to hydroxycarbamide	As per scope	HC intolerance definition varies
Intervention	Ruxolitinib + established clinical practice	As per scope	No comment
Comparators	Established clinical practice without ruxolitinib (best available therapy): • Hydroxycarbamide • Interferon alfa • Radioactive phosphorus • Busulfan • Anagrelide	Excludes radioactive phosphorus	HC and IFN-alpha main comparators
Outcomes	• CHR • TTD • Mortality • Symptom relief • Thrombosis • Progression to AML/MF • Adverse events • HRQoL	OS instead of mortality	No comment
Subgroups	People with and without splenomegaly	Add high-risk subgroup	No comment

Abbreviations: AML, acute myeloid leukaemia; CHR, complete haematological response; HC, hydroxycarbamide; HRQoL, health related quality of life; IFN, interferon; MF, myelofibrosis; OS, overall survival; PV, polycythaemia vera; TTD, time to treatment discontinuation

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

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

RESPONSE and RESPONSE-2 trial results

More people achieved HCT control with ruxolitinib than with best available therapy in RESPONSE and RESPONSE-2

RESPONSE (with splenomegaly)	Ruxolitinib (n=110)	BAT (n=112)	Difference
Primary outcome: Primary response at week 32 (HCT control and spleen volume)	22.7%	0.9%	20.02 (95% CI 12.22 to 27.82); p<0.001
People achieving HCT control	60.0%	18.8%	-
People with ≥35% spleen volume reduction	40.0%	0.9%	-
Overall survival at 5 years	91.9%	-	-

RESPONSE-2 (without splenomegaly)	Ruxolitinib (n=74)	BAT (n=75)	Difference
Primary outcome: People achieving HCT control at week 28	62.2%	18.7%	OR: 7.28 (95% CI 3.43 to 15.45) p<0.0001
Overall survival at 5 years	96.0%	-	-

NICE

Abbreviations: BAT, best available therapy; HCT, haematocrit; OR, odds ratio

MAJIC-PV trial results

More people achieved complete haematological remission at 1 year with ruxolitinib than with best available therapy in MAJIC-PV

MAJIC-PV	Ruxolitinib (n=93)	BAT (n=87)	Difference
Primary outcome: People achieving complete haematological remission in year 1	43%	26%	Adjusted OR 2.12 (90% CI 1.25 to 3.60); p=0.02
Overall survival at 3 years	88%	87%	-
Progression-free survival at 3 years	84%	75%	-

Longer-term survival data is also available from MAJIC-PV at 5-years of follow-up but overall and progression-free survival differences were not significant:

- **Overall survival HR:** 0.73 (95% CI: 0.36 to 1.50); p=0.39
- **Progression-free survival HR:** 0.64 (95% CI: 0.36 to 1.15); p=0.13

NICE Abbreviations: BAT, best available therapy; HCT, haematocrit; HR, hazard ratio; OR, odds ratio

Key issue: Generalisability of trial population (1)

MAJIC-PV was a UK only trial not confounded by crossover

Background

- RESPONSE trial included 3 UK sites and RESPONSE-2 trial included no UK sites
- MAJIC-PV trial (included only UK sites) is used by company only for high-risk subgroup
- Crossover to ruxolitinib was permitted in RESPONSE and RESPONSE-2 trials from week 32 and 28 respectively, 88% and 77% of people crossed over, respectively
- So survival data from RESPONSE and RESPONSE-2 is confounded by crossover

Company

- Experts confirmed population recruited in MAJIC-PV trial most likely reflects UK population, but RESPONSE trials' populations are also reflective of the UK population
- All 3 trials represent people who would benefit from ruxolitinib and are relevant
- Adjustment for crossover not feasible due to low frequency of deaths so ITC developed for confounded RESPONSE OS data (ITC not used to inform base case)
- There are limitations with the ITC for crossover but results support the survival benefits of ruxolitinib over BAT

Abbreviations: BAT, best available therapy; ITC, indirect treatment comparison; OS, overall survival

Key issue: Generalisability of trial population (2)

Clinical experts agree all trials are relevant but to different degrees

EAG comments

- Clinical experts advising the EAG agree that all 3 trial populations are reflective of UK patients, but the MAJIC-PV population is most reflective due to the age of participants
- Not clear how far MAJIC-PV population represents a high-risk subgroup, baseline characteristics appear similar to other trials, but mortality rate was substantially higher
- Lack of standardised definitions of intolerance to HC in practice and trials
- RESPONSE/-2 limited by crossover, MAJIC-PV provides unconfounded evidence

Clinical experts

- One expert agreed with the view that the MAJIC PV patient population more closely resembles the appropriate population for review, also preferable due to no crossover
- RESPONSE/-2 entry criteria very specific (number of venesections, splenomegaly etc)
- Another expert thought all three trials were relevant for the UK population

Which of the 3 ruxolitinib trials should be used for decision-making?

Abbreviations: HC, hydroxycarbamide; NHS, National Health Service

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview (1)

Two models developed based on available data

Figure: Model structure the company's models

For each state, models capture:

- Treatment related AEs
- Key complications: thromboembolic events, bleeding/ haemorrhage, progression to myelofibrosis/cancers
- Phlebotomy
- HRQoL and resource use

Table: Differences across the company's models

	RESPONSE/-2 model	MAJIC-PV model
Subgroups	With/without splenomegaly	High-risk PV
Model type	State transition model	Partitioned survival model
BAT sub-health states	• First BAT regimen • Second+ BAT regimen • No treatment	None

Key issue:
Company's model structure to be discussed…

Abbreviations: AE, adverse event; BAT, best available therapy; HC, Hydroxycarbamide; HRQoL, health related quality of life; PSM, partitioned survival model; PV, polycythaemia vera; STM, state transition model

How company incorporated evidence into model

Input	RESPONSE/RESPONSE-2 (primary model)	MAJIC-PV (high-risk subgroup model)
Baseline info	RESPONSE and RESPONSE-2 trials	MAJIC-PV trial
TTD	**Ruxolitinib arm:** RESPONSE/-2 trial data **Comparator arm:** MAJIC-PV data by BAT line	**Ruxolitinib arm:** OS data adjusted with HR for TTD vs OS
Overall survival	**Ruxolitinib arm:** estimated from RESPONSE pre- and post-discontinuation survival **Comparator arm:** HR for BAT vs ruxolitinib from MAJIC-PV applied to ruxolitinib arm OS	**Ruxolitinib arm:** HR for ruxolitinib vs BAT from MAJIC-PV applied to comparator arm OS **Comparator arm:** Extrapolation of MAJIC-PV KM data for BAT
Events	Incidence rates calculated from RESPONSE, RESPONSE-2, MAJIC-PV trials	
Utilities	MF-8D scores from RESPONSE and RESPONSE-2 trials	
Costs	NHS reference costs 2020/2021, PPSRU 2021, BNF, eMIT	

Abbreviations: BAT, best available therapy; HR, hazard ratio; NHS, National Health Service; OS, overall survival; TTD, time to treatment discontinuation

Company's model overview (2)

Inputs and assumptions that affects costs and QALYs

- **Technology affects costs by:**
  - Higher cost of ruxolitinib versus other treatments
  - Lower costs from reduced use of phlebotomy, follow-up and monitoring after 6 months
  - Lower costs from reduced treatments for other conditions and adverse effects
  - Higher costs from treatment for skin cancer, AML and myelodysplastic syndrome
- **Technology affects QALYs by:**
  - Lower mortality rate while people are being treated with ruxolitinib
  - Improved health-related quality of life while people are being treated with ruxolitinib
  - Small utility increase from reduced incidence of phlebotomy and adverse effects
- **Assumptions with the greatest ICER effect:**
  - Hazard ratio for overall survival
  - Assumptions about waning of the treatment effect for overall survival
  - Distribution used for extrapolation of time to discontinuation of ruxolitinib
  - Use of EQ-5D or MF-8D utility estimates

Abbreviations: AML, acute myeloid leukaemia; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Key issue: Company's model structure (1)

The company developed a new model in response to EAG requests

Background on issues raised by the EAG

- Model health states are based on treatment stages instead of disease stages
- Progression outcomes are more prognostic of long-term survival than treatment stages

Company

- Developed new progression-based model to address EAG's concerns
- Original model is maintained in base case, ICERs are lower in the new model

EAG comments

- EAG favour new model as it reflects disease progression directly, but EAG do not adopt the new model in its base case due to limited opportunity to review
- Seek input from clinical experts or external data to validate new model outcomes

Clinical experts

- Prefer a model based on clinical events, but treatment usually follows disease changes

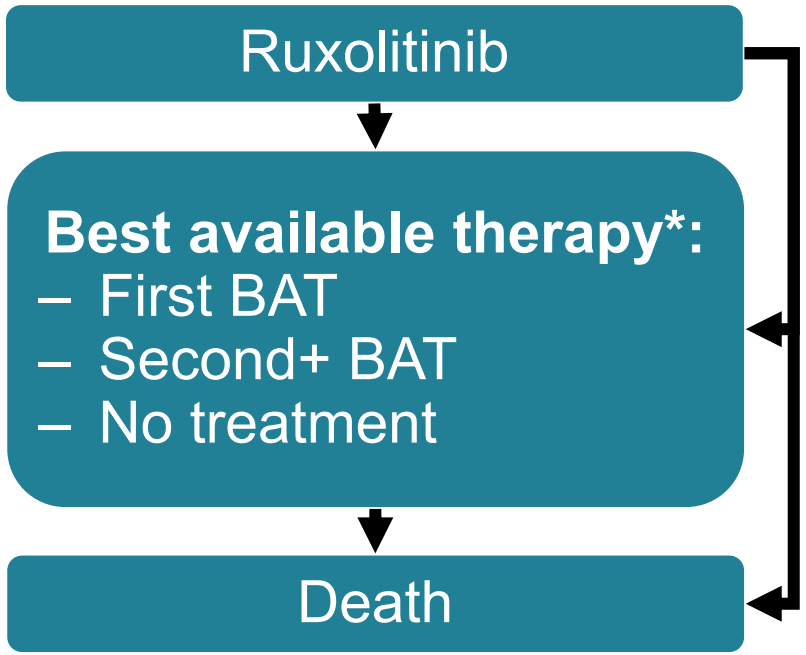
Abbreviation: ICER, incremental cost-effectiveness ratio

New model schematic shown on next slide

Key issue: Company's model structure (2)

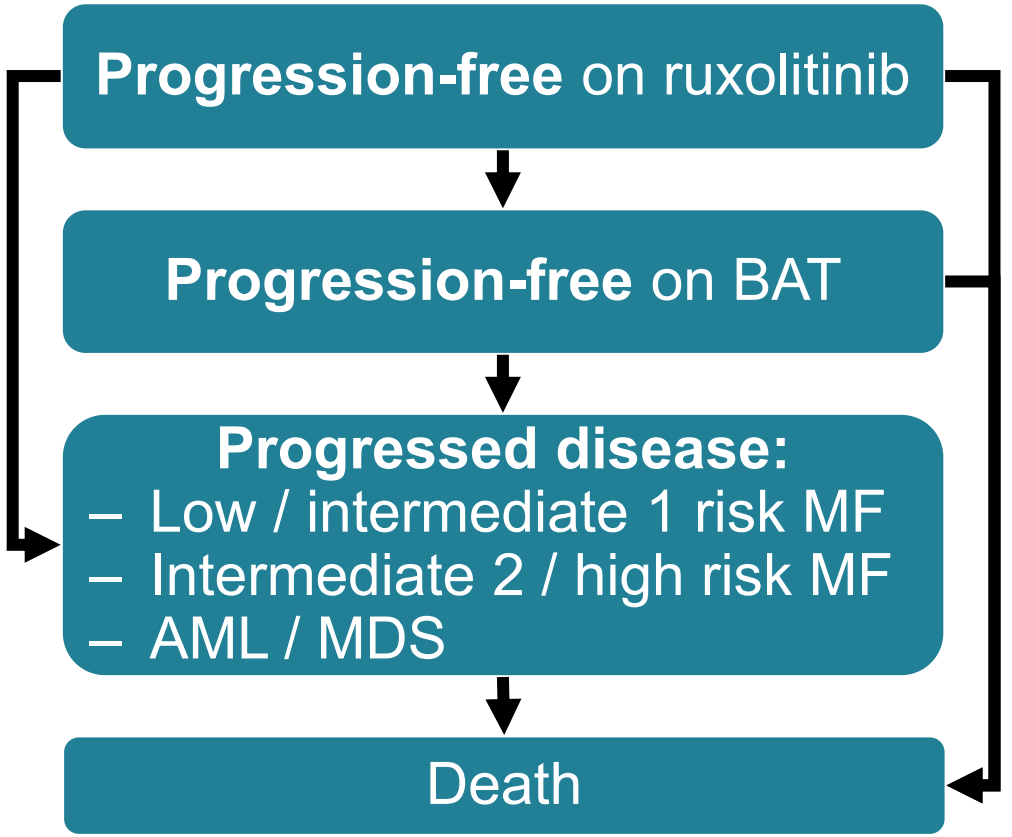
Company's new model is not used in its base case

Original company model



*Substates for RESPONSE/-2 populations only

New company model



New model not used in company or EAG base case due to limited time to review and validate outcomes

Is the company's original model appropriate for decision-making?

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

Key issue: Treatment effect for overall survival (1)

Company used time-varying hazards and treatment waning to model OS

Background

- MAJIC-PV trial data used to estimate HR for OS due to crossover in RESPONSE trials

Company

- Estimated time-varying hazard ratios using a piecewise Cox proportional hazards model
- Larger effect after 3 years based on expert advice, visual inspection and trial results
- Assume treatment effect diminishes linearly and entirely from 5 years to 20 years

EAG comments

- Methods to apply piecewise HRs are appropriate and may be clinically plausible
- Confidence intervals for constant HRs are wide, piecewise HR intervals are wider
- High uncertainty over the treatment effect so EAG prefers constant HR from MAJIC-PV
- Experts identified no reason to assume a loss of effect with long-term ruxolitinib
- Given uncertainty, EAG keep treatment waning, removing it has large impact on ICERs

Company: Treatment waning should not be combined with conservative constant HR

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival

Key issue: Treatment effect for overall survival (2)

Hazard ratios from MAJIC-PV and clinical experts views on treatment waning

Clinical experts

- Difficult to judge waning of treatment effect when some studies employed crossover
- Personal experience of people doing very well on ruxolitinib, mean age is approximately 67
- No known evidence for treatment resistance, ruxolitinib known to have a sustained benefit

Company: challenging to show a survival gain in PV due to the comparably favourable prognosis of patients with PV and low number of events in trials reducing statistical power

Figure: OS data from MAJIC-PV

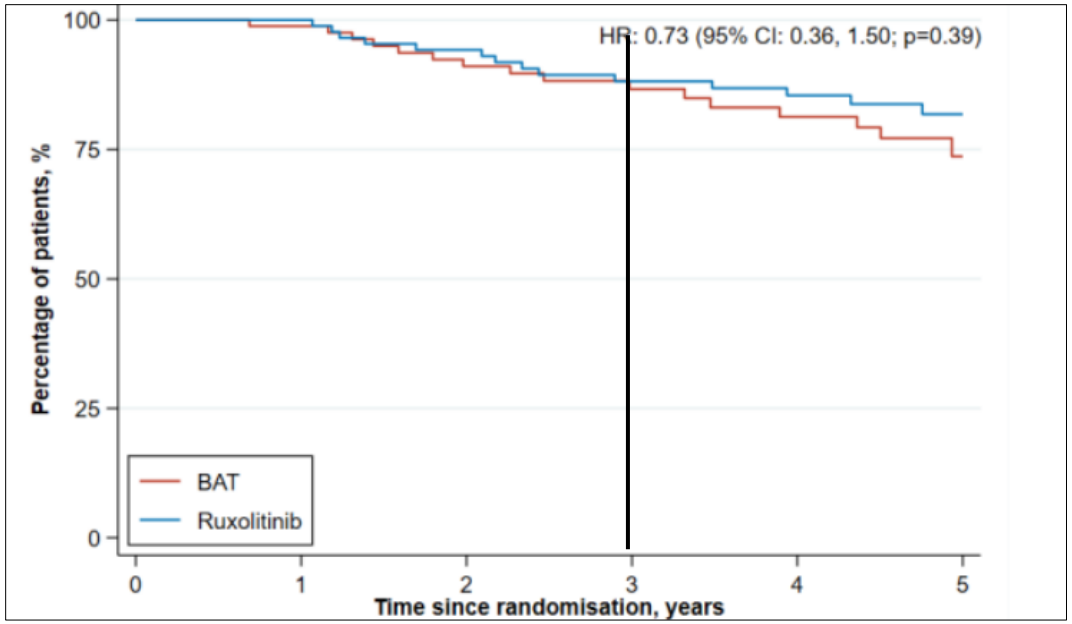


Table: HRs for OS for ruxolitinib vs BAT

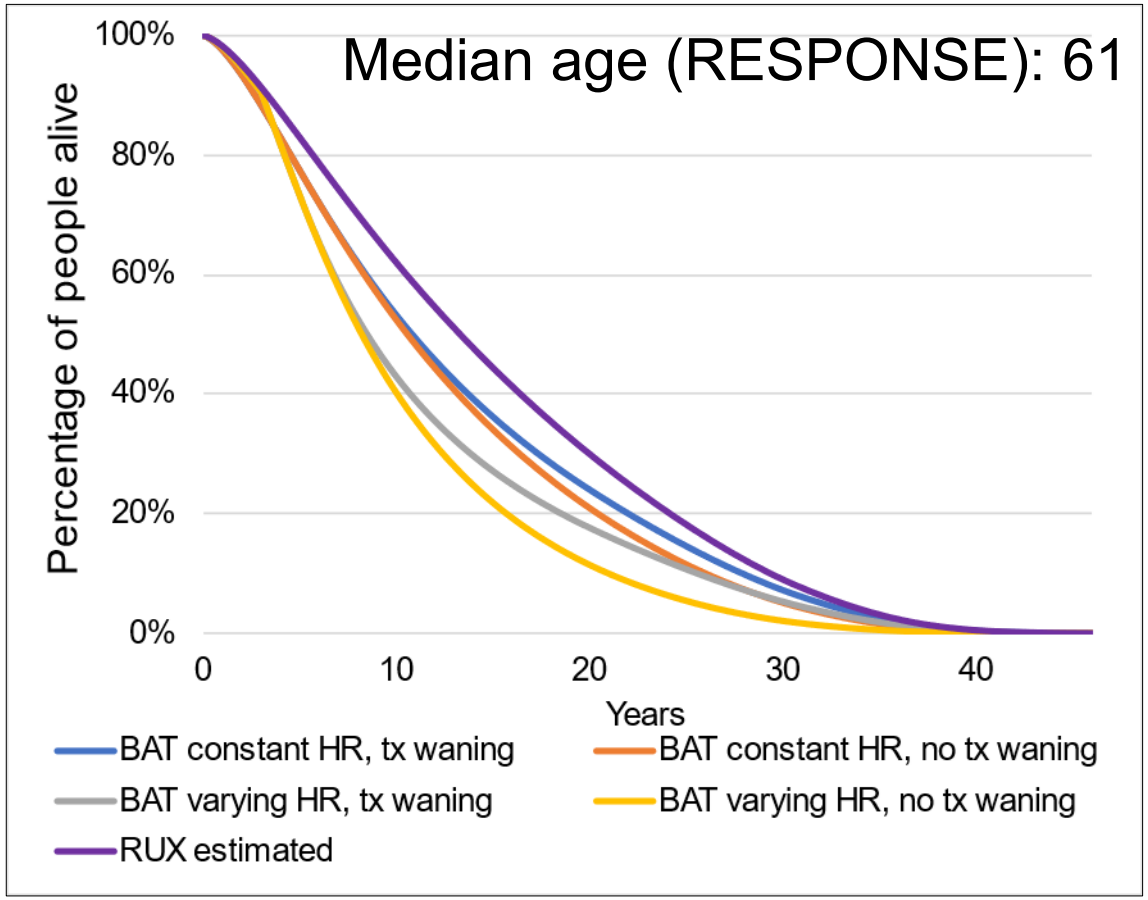
Source	Hazard ratios [95% CI]
Constant HR from MAJIC-PV (EAG)	**All years:** 0.73 [0.36-1.50]
Time-varying HR from MAJIC-PV (company)	**0-3 years:** 0.91 [0.38-2.18] **3-5 years:** 0.45 [0.13-1.61]

Abbreviations: BAT, best available therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival

Key issue: Treatment effect for overall survival (3)

Overall survival estimates for the splenomegaly group, company base case

Figure and Table: Modelled OS from RESPONSE for different assumptions and treatment arm



Year	1	5	20
BAT constant HR, tx waning	98%	77%	24%
BAT constant HR, no tx waning	98%	77%	21%
BAT varying HR, tx waning	98%	73%	18%
BAT varying HR, no tx waning	98%	73%	11%
RUX estimated	98%	83%	30%

Estimated from pre- and post-discontinuation survival; MAJIC-PV HR applied to get BAT OS

Do these survival curves look plausible?

What assumptions should be made for OS treatment effect in the model?

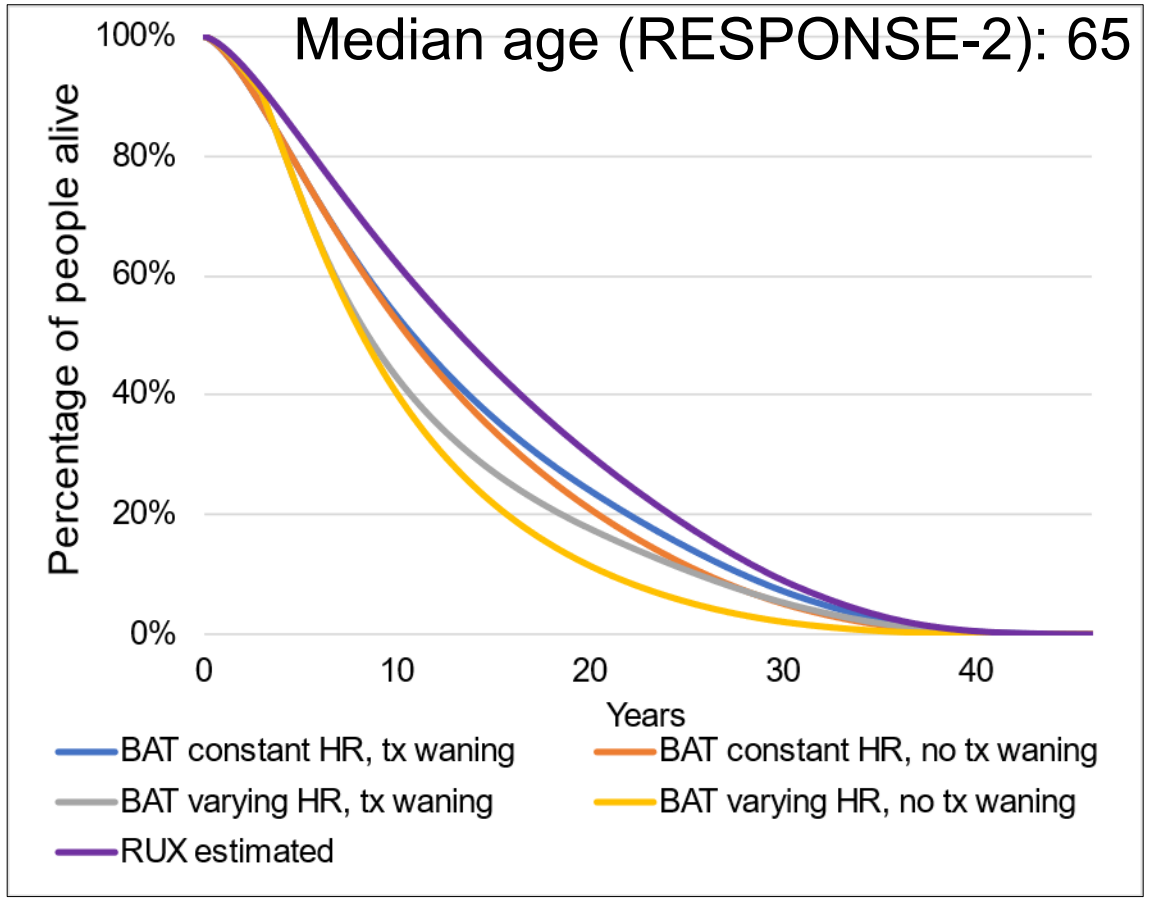
NICE

Abbreviations: BAT, best available therapy; KM, Kaplan-Meier; OS, overall survival; RUX, ruxolitinib; tx, treatment

Key issue: Treatment effect for overall survival (4)

Overall survival estimates for without splenomegaly group, company base case

Figure and Table: Modelled OS from RESPONSE-2 for different assumptions and treatment arm



Year	1	5	20
BAT constant HR, tx waning	98%	84%	31%
BAT constant HR, no tx waning	98%	84%	27%
BAT varying HR, tx waning	98%	81%	25%
BAT varying HR, no tx waning	98%	81%	17%
RUX estimated	99%	88%	37%

Estimated from pre- and post-discontinuation survival; MAJIC-PV HR applied to get BAT OS

Do these survival curves look plausible?

What assumptions should be made for OS treatment effect in the model?

Abbreviations: BAT, best available therapy; KM, Kaplan-Meier; OS, overall survival; RUX, ruxolitinib; tx, treatment

Key issue: Utility values (1)

Company used MF-8D for estimating health utilities for the economic model

Background

- Company use utility estimates for MF-8D derived from 3 items from EORTC QLQ-30 and 5 items from MPN-SAF data from the RESPONSE trial
- NICE reference case stipulates empirical evidence needed to deviate from EQ-5D use

Company

- Based on RESPONSE-2 data, evidence of the unsuitability of EQ-5D for PV:
  - **Ceiling effect:** [redacted] of people reported no problems in all 5 EQ-5D measures at baseline compared to [redacted] for MPN-SAF
  - **Construct validity:** EQ-5D lacks construct validity as convergence is inconsistent across MPN-SAF domains at baseline
  - **Responsiveness:** change in scores for MPN-SAF were medium to large compared to small to very small for EQ-5D
- 2 NICE myelofibrosis appraisals (TA386 and TA756) where use of MF-8D accepted
- Very similar nature of symptoms for PV and myelofibrosis

Abbreviations: EORTC: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; MPN-SAF, myeloproliferative neoplasm symptom assessment form total symptom score; PV, polycythaemia vera

Key issue: Utility values (2)

EAG finds there is not sufficient evidence to not use EQ-5D

EAG comments

- Company's evidence fails to reject the use of EQ-5D in the EAG base case
- Comparison of EQ-5D and MPN-SAF showed strong correlation thus overall utility values would be similar
- Estimated utility differences in treatment arms are similar between EQ-5D and MF-8D

Patient and clinical experts

- Symptom improvements for people with PV are highly underestimated in EQ-5D
- EQ-5D not validated in PV, MF-8D reflects the lived experience of people with PV

Source	Estimated utility gain for ruxolitinib vs BAT (RESPONSE)
MF-8D	[redacted]
EQ-5D	[redacted]

Is EQ-5D or MF-8D more appropriate?

Abbreviations: BAT, best available therapy; CI, confidence interval; MPN-SAF, myeloproliferative neoplasm symptom assessment form total symptom score, PV, polycythaemia vera

Key issue: Extrapolating TTD for ruxolitinib

EAG's preferred approach is different to the company

Figure: Ruxolitinib TTD without splenomegaly

Figure: Ruxolitinib TTD with splenomegaly

Background

- Results sensitive to ruxolitinib TTD which impacts survival, treatment utility and costs

Company

- Odds spline with one knot chosen due to visual/statistical fit and clinical plausibility
- Statistical fit similar across distributions
- Experts noted discontinuation would be higher early in treatment before stabilising

EAG comments

- Prefer Weibull distribution because it has best statistical fit for RESPONSE and similar fit for RESPONSE-2 trial data

Is odds spline or Weibull extrapolation for ruxolitinib TTD preferred?

Abbreviations: KM, Kaplan-Meier; OS, overall survival; TTD, time to treatment discontinuation

Summary of company and EAG base case assumptions

Table: Difference in assumptions in company and EAG base cases with **large** ICER impacts

Assumption	Company base case	EAG base case
Model structure	Original model	Original model (progression-based model preferred but not used)
Overall survival HR	Time-varying with waning	Constant with waning
Source of utility	MF-8D	EQ-5D

Table: Difference in assumptions in company and EAG base cases with **minimal** ICER impacts

Assumption	Company base case	EAG base case
TTD extrapolation	Odds spline, one knot	Weibull distribution
General population mortality	Constraint included after 5 years	Constraint applied for full time horizon
BAT substates	3 substates for RESPONSE trials	No substates (original model)
Thromboembolic event costs	Emergency department visit	Emergency department visit + costs for additional tests

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Abbreviations: BAT, best available therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; TTD, time to treatment discontinuation

Cost-effectiveness results

ICERs are reported in PART 2 slides due to confidential discounts

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Cost-effectiveness results

Summary of cost-effectiveness results:

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

Scenarios applied to company base case	Scenarios applied to EAG base case
Ruxolitinib TTD Weibull extrapolation	Ruxolitinib TTD odds spline extrapolation
MAJIC-PV: constant OS HR	MAJIC-PV: time-varying OS HR
No BAT partition of health states	BAT partition of health states
EQ-5D utility values	MF-8D utility values
EAG's thromboembolic event costs	Company's thromboembolic event costs
Treatment waning (from 10 to 50 years)	Treatment waning (from 10 to 50 years)
Company's new model structure	Company's original model structure
Remove impact of key events	Remove impact of key events

Abbreviations: BAT, best available therapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; TTD, time to treatment discontinuation

Key questions for committee to answer in Part 2

Parameter	Key question	Scenarios	ICER impact
Generalisability	Which models should be used for decision making?	• All 3 subgroups/trials • MAJIC-PV only	Large ↓
Company's model	Company's original model acceptable?	• Original model • New model	Large ↓
Treatment effect	What assumptions should be made for OS treatment effect in the model?	• Time varying OS HRs • Constant OS HRs • Treatment waning • No treatment waning	Large ↑
Utility estimates	EQ-5D or MF-8D?	• EQ-5D • MF-8D	Large ↑
Treatment discontinuation	Odds spline or Weibull for ruxolitinib TTD?	• Odds spline • Weibull	Small ↕

Arrows indicate direction of impact on company base case (multi-directional arrows mean direction of impact varies by subgroup)

NICE

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

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Thank you.