NICE National Institute for Health and Care Excellence

[Public observer slides - redacted]

Fedratinib for splenomegaly and symptoms in myelofibrosis [ID1501]

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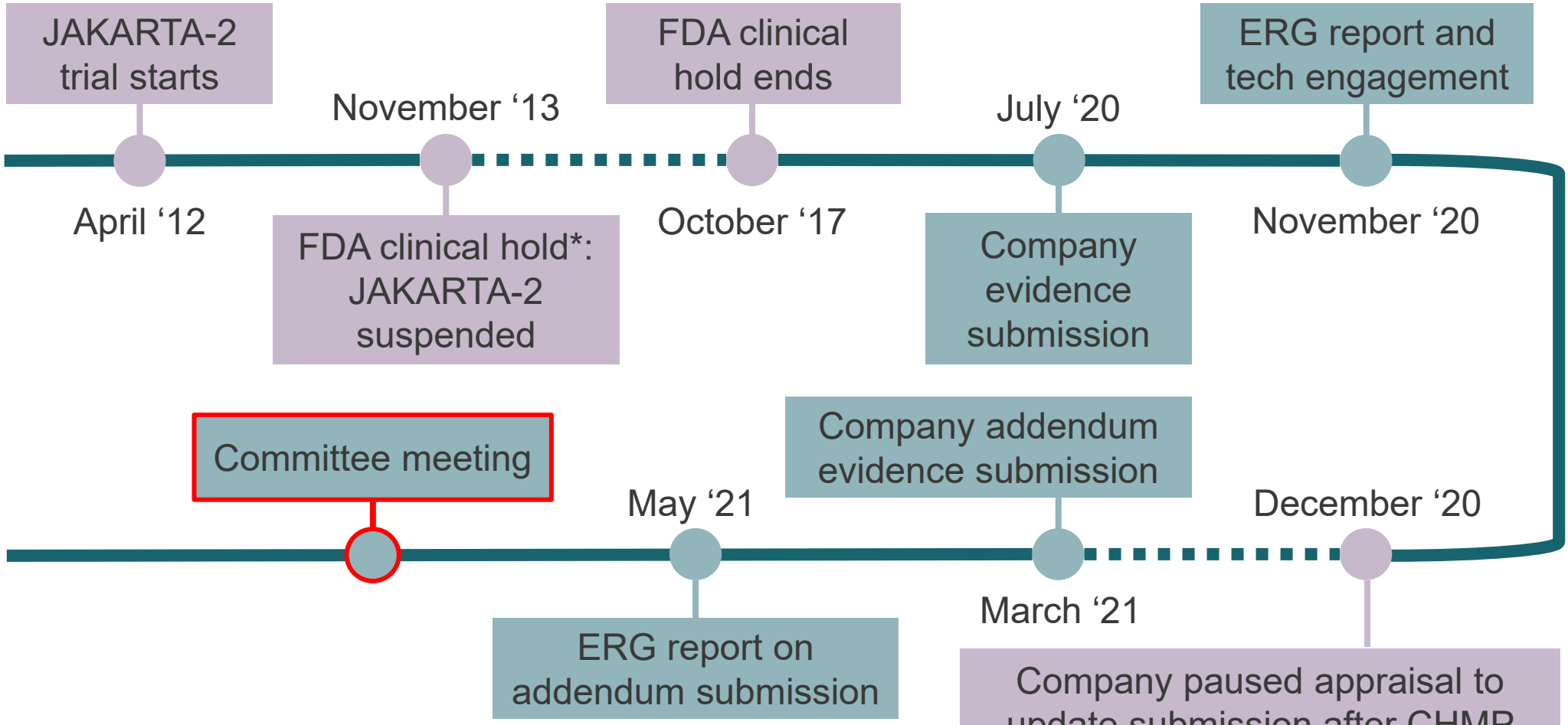
Company: Celgene, a BMS Company

ACM 1: 16 June 2021

Fedratinib history



* Fedratinib treatment stopped for patient safety. 8 cases of suspected Wernicke’s encephalopathy. Found to be a consequence of gastrointestinal adverse events in undernourished patients

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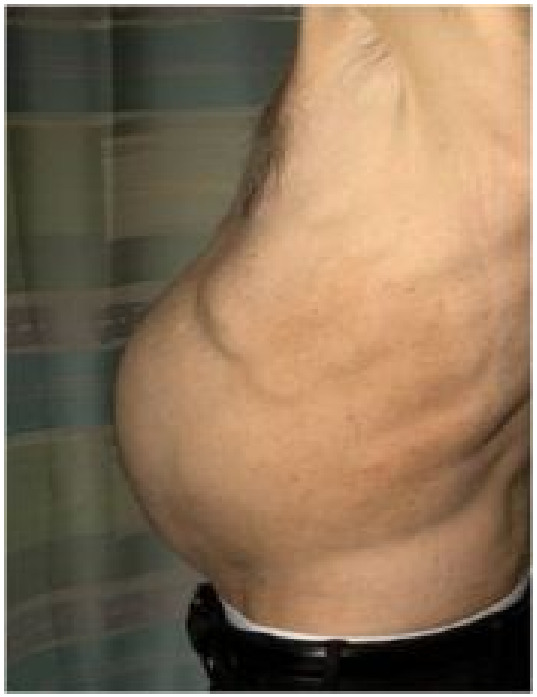
Regulatory event Appraisal event

CHMP, Committee for Medicinal Products for Human Use; FDA, Food and Drug Administration

Myelofibrosis

- Bone marrow cancer in which the marrow is replaced by scar (fibrous) tissue. Around 2 to 3 people per 100,000 are diagnosed with myelofibrosis every year. Presents as:
  - Primary (known as chronic idiopathic myelofibrosis)
  - Secondary to polycythaemia vera (bone marrow makes too many red blood cells) or essential thrombocythaemia (bone marrow makes too many platelets)
- The bone marrow produces fewer blood cells. To compensate, blood cell production occurs in the spleen and liver, causing these organs to enlarge
- Spleen enlargement (splenomegaly) may cause abdominal pain, dyspnoea (shortness of breath), early satiety (feeling full) and faecal incontinence, along with progressive anaemia



Adapted from Fuerst, M. *JAK inhibitor ruxolitinib improves treatment landscape in MF.* Haematology Times. Online November 2011. Image courtesy of S. Verstovsek

- About half of people with myelofibrosis have a mutation in the JAK2 protein
- To guide treatment, myelofibrosis is classified into low-, intermediate- and high-risk categories according to the Dynamic International Prognostic Scoring System (DIPSS)*
- Median survival is 5 years from onset, but variation is wide (some have rapidly progressing disorder with short survival)

* Based on prognostic factors: age, constitutional symptoms, haemoglobin level, leukocyte count, and circulating blasts. JAK2, Janus kinase 2

Fedratinib (Inrebic, Celgene)

Company's positioning is narrower than full marketing authorisation

Marketing authorisation (granted 08/02/2021)	'For the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor-naïve or who have been treated with ruxolitinib.' Fedratinib has not been studied in patients with platelets <50 x 10^9 /L at baseline and may not be appropriate for use in this population
Mechanism of action	Kinase inhibitor with activity against wild-type and mutationally activated JAK2
Administration	Single oral dose of 400 mg daily (4 x 100 mg capsules) taken with or without food
Price	• The list price is [redacted] per pack (120 x 100 mg capsules) • [redacted] 52-week cost (about 1 year) • Simple PAS discount approved

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JAK, Janus kinase; PAS, patient access scheme

Background

Comparator	Best available therapy (BAT, 88.5% ruxolitinib)
Clinical trial	JAKARTA-2, single-arm phase 2 study (N=97, intermediate-2/high-risk group n=81)
Key results (CHMP response definition*)	Proportion of patients with spleen response after 6 cycles: ITT population, 22.7% and **intermediate-2/high-risk population,** [redacted]
ITC for response with BAT	No direct evidence vs. BAT, therefore company did a matching-adjusted indirect comparison (MAIC)
ITC result vs. BAT	Spleen/symptom response at 24 weeks: OR [redacted] (95% confidence interval [redacted])
BAT overall survival	Schain et al. 2019 (post-ruxolitinib discontinuation)
Model	Discrete event simulation. 5 health states: BAT, fedratinib, BAT (post-fedratinib), supportive care, death. 2 event types: treatment discontinuation and death
Company ICER**	£24,784/QALY gained
ERG-preferred ICERs**	£109,316/QALY gained (switch to ruxolitinib after relapse) £114,005/QALY gained (remain on fedratinib after relapse)

* Counting people responding after up-titration as non-responders

** Accounting for confidential discounts for other treatments increases ICERs

CHMP, Committee for Medicinal Products for Human Use; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intent to treat; OR, odds ratio; QALY, quality-adjusted life year

Myelofibrosis treatment pathway

Company positions fedratinib in people who have had ruxolitinib

People with intermediate-2 or high-risk primary, post-essential thrombocythaemia or post-polycythaemia vera myelofibrosis not eligible for ASCT

- Ruxolitinib (TA386) → Fedratinib
- ~~Fedratinib~~ (*Company omits from positioning*) → Suboptimal ruxolitinib
- Best available therapy* → Best available therapy excluding ruxolitinib

ERG

Prefer separate comparators for people who continue vs discontinue ruxolitinib

Clinical experts

For disease that is relapsed/refractory to ruxolitinib most (>80%) would continue to have ruxolitinib. People who cannot tolerate ruxolitinib are likely a clinically different group – most (>90%) would stop ruxolitinib and potentially move to experimental therapy

Company

- Not possible to split population in JAKARTA-2 in line with ERG comments
- No internationally recognised criteria for intolerance/resistance (there could be overlap)

Should people who continue vs discontinue ruxolitinib be considered separately?

* BAT includes: hydroxycarbamide, other chemotherapies, androgens, radiation therapy, RBC transfusion

ASCT, allogenic stem cell transplant. RBC, red blood cell

Patient and carer perspectives

Myelofibrosis is a rare cancer with limited treatment options. Experience with ruxolitinib varies. Additional treatment options are needed for people with disease that becomes resistant to ruxolitinib

Common symptoms include:

- **Fatigue** or debilitating exhaustion that reduces quality of life. Can be associated with feelings of guilt or frustration
- **Enlarged spleen** associated with pain, discomfort and early satiety
- **Severe itching** described as 'being rolled naked in nettles'
- **Night sweats**
- **Bone pain** not alleviated by painkillers
- **Mental health** challenges such as worrying about limited treatment options and worsening condition

> "My fatigue and anaemia had a lot of impact on my high intensity job as a doctor, I had to reduce hours"

> "My work efficiency fell to 50-60%. I recognised that any further deterioration to my health would result in my giving up work"

> "I participate[d] in the JAKARTA trial. My symptoms lessened – spleen reduced, appetite improved, fatigue lessened and I started to lead a normal life, working full-time"

Clinical perspective

- Views from 2 consultant haematologists
- Unmet need for new treatment options after ruxolitinib. In most cases the disease does not adequately respond to ruxolitinib (or subsequently loses response), and people having ruxolitinib often have side effects which can lead to discontinuation
- Current care pathway is reasonably well defined. But, myelofibrosis is rare and treatment can vary by haematologist's experience. Physicians are also not used to defining ruxolitinib intolerance or resistance
  - Aims of treatment: to improve symptoms, to reduce spleen size, and to improve life expectancy
- People with intermediate-2 or high-risk disease are generally treated with ruxolitinib
  - "*Often clinicians do not discontinue ruxolitinib as patients often get worsened symptoms and spleen enlargement (so-called ruxolitinib withdrawal syndrome if the drug is withdrawn)*"
- Fedratinib could improve health-related quality of life. Particularly impactful for people with ongoing splenomegaly or symptoms while on ruxolitinib, or for whom ruxolitinib is poorly tolerated

JAKARTA-2: phase 2, single-arm study

Population (N=97, int-2/high risk n=81)	• Primary myelofibrosis (MF), post-polycythaemia vera (PV) myelofibrosis, post-essential thrombocythemia (ET) myelofibrosis • Intermediate-1 (symptomatic)/intermediate-2/high-risk MF (DIPSS) • Previously treated with ruxolitinib (≥14 days unless intolerant) • Platelet count ≥50 x 10^9/L	
Locations	31 academic hospitals in 9 countries (including the UK)	
Characteristics (ITT population)	• Disease type • Risk status • ECOG • Median age • Male	Primary MF: 55%, Post-PV: 26%, Post-ET 20% Intermediate-1: 17%, Intermediate-2: 48%, high: 35% Performance status (PS) 0: 27%, PS 1: 46%, PS 2: 24% 67 years 55%
Intervention	Fedratinib	
Follow up	6 x 28-day cycles (6 months), plus follow-up visit 30 days after last dose. Median follow up 6 months, interquartile range 3.9 to 8.9 months	
Clinical experts	Eligibility criteria for JAKARTA-2 were quite unrestrictive - patient population is reasonably generalisable by demographics and disease characteristics. Life expectancy would be similar to the current NHS population	
ERG	Results from phase 2 studies can overestimate treatment effects	

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Are the results from JAKARTA-2 generalisable to the NHS in England?

DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; PS, performance status

CHMP requested analyses counting patients who responded after up-titration as non-responders

Background

- CHMP noted uncertainty about clinical benefit from up-titration (>400 mg/day) and requested analysis for fedratinib response excluding up-titrated patients
- JAKARTA-2 study permitted dose escalation from 400mg to 600mg per day within first 6 cycles for patients with <50% reduction in spleen size
- 29 patients had dose up-titrations (n=20 up to 500mg, and n=9 up to 600mg)
- Company/ERG base cases use CHMP response definition

ERG

- SmPC does not explicitly state that patients cannot have more than 400 mg, and does not mention dose escalation in absence of spleen/symptom response
- In ongoing FREEDOM-2 study, dose cannot exceed 400 mg daily

If recommended, NHS England commissioning criteria would reflect that NICE considered analyses without dose escalation

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency

JAKARTA-2 results: end of cycle 6*

Outcome	ITT population (n=97) n (%)	Intermediate-2/high-risk subgroup (n=81)	
		Including up-titrations within first 6 cycles, n (%)	CHMP definition: Up-titrations counted as non-responders, n (%)
Primary outcome			
Spleen response (≥35% spleen volume reduction)	30 (30.9%)	[redacted]	[redacted]
Secondary outcomes			
Symptom response (≥50% reduction in total symptom score)	[redacted]	[redacted]	[redacted]
Duration of spleen response (median)	Not reached	N/A	N/A
Spleen response rate by palpation (≥50% reduction in size)	30 (31%)	N/A	N/A
% change of spleen volume	-38.0%	N/A	N/A

*13 patients did not reach end of cycle 6 because of the clinical hold

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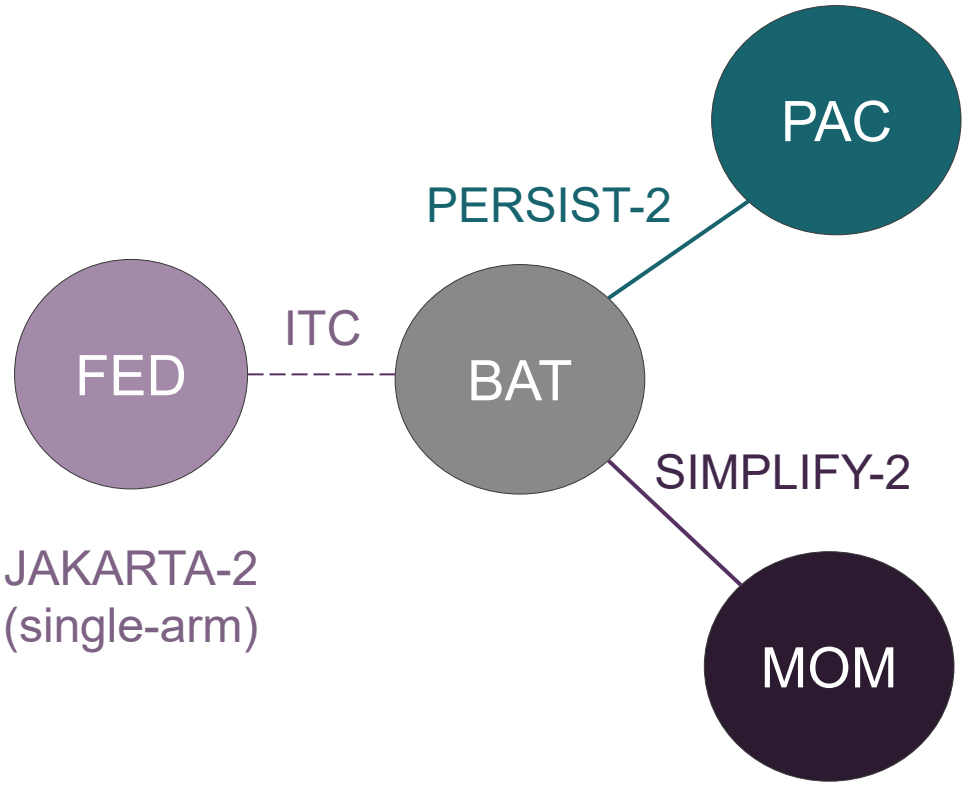
Note: Symptom response based on myelofibrosis symptom assessment form (MF-SAF)
CHMP, Committee for Medicinal Products for Human Use; ITT, intent to treat

Indirect treatment comparison for response

Background

JAKARTA-2 was a single-arm study. To compare the treatment effect of fedratinib versus BAT for response rate, indirect treatment comparisons were conducted using BAT arm data from PERSIST-2 and SIMPLIFY-2



Company

Conducted 5 types of ITCs for spleen or symptom response:

1. Naïve comparison with PERSIST-2
2. Naïve comparison with SIMPLIFY-2
3. **MAIC with SIMPLIFY-2 (adjusted for ECOG PS and DIPSS) (company base case)**
4. STC with SIMPLIFY-2 (adjusted for ECOG PS and DIPSS)
5. MAIC with SIMPLIFY-2 (adjusted for ECOG PS, DIPSS and transfusion dependence)

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BAT, best available therapy; PAC, pacritinib; FED, fedratinib; MOM, momelotinib; ITC, indirect treatment comparison; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison

Indirect treatment comparison for response

Company

- Given JAKARTA-2 small sample size, pragmatic approach to identify variables for the MAICs:
  - If clinically meaningful imbalance by external haematologist and,
  - Identified as important prognostic factor
- Haematologist identified ECOG PS, DIPSS, transfusion dependence
- Number of 'spleen/symptom' responders not reported in SIMPLIFY-2. Minimum and maximum analyses were run (see table)

ERG

- Potential differences in patient populations beyond adjusting for prognostic factors
- Ignoring predictor variables that are individually balanced may not achieve balance overall
- Evidence is supportive of better response rate for fedratinib, but results are not robust

MAIC results (FED vs BAT): *SIMPLIFY-2, adjusting for DIPSS and ECOG PS*

BAT response	Odds ratio (CI)
Minimum	[redacted] ([redacted] to [redacted])
Maximum	[redacted] ([redacted] to [redacted])
Average	[redacted] ([redacted] to [redacted])

Spleen/symptom response probabilities at 24 weeks (used in model)

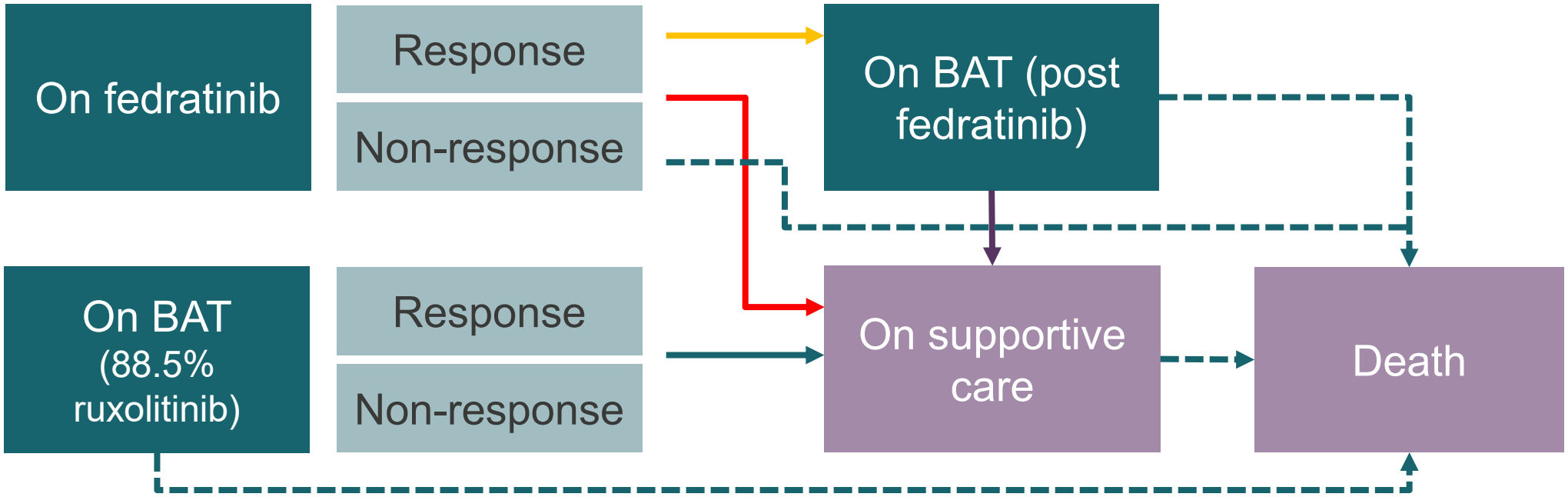
Fedratinib	BAT
[redacted]	[redacted]

Calculated by applying the average BAT response odds ratio to the fedratinib response probability

Is the company's MAIC appropriate for decision making?

BAT, best available therapy; CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MAIC, matching-adjusted indirect comparison; FED, fedratinib; STC, simulated treatment comparison

Company's discrete event simulation model



- Sampling from a TTD curve at model entry decides time of discontinuation. At discontinuation a proportion of responders and non-responders transition to BAT
- Remaining proportion of patients who do not transition to BAT at discontinuation
- A proportion is specified for the remaining time alive spent between BAT and supportive care
- Sampling from a TTD curve at model entry decides time of discontinuation
- Transition to death: For fedratinib, sampling from post-discontinuation OS curve at discontinuation decides time of death. For BAT, sampling from an OS curve at model entry

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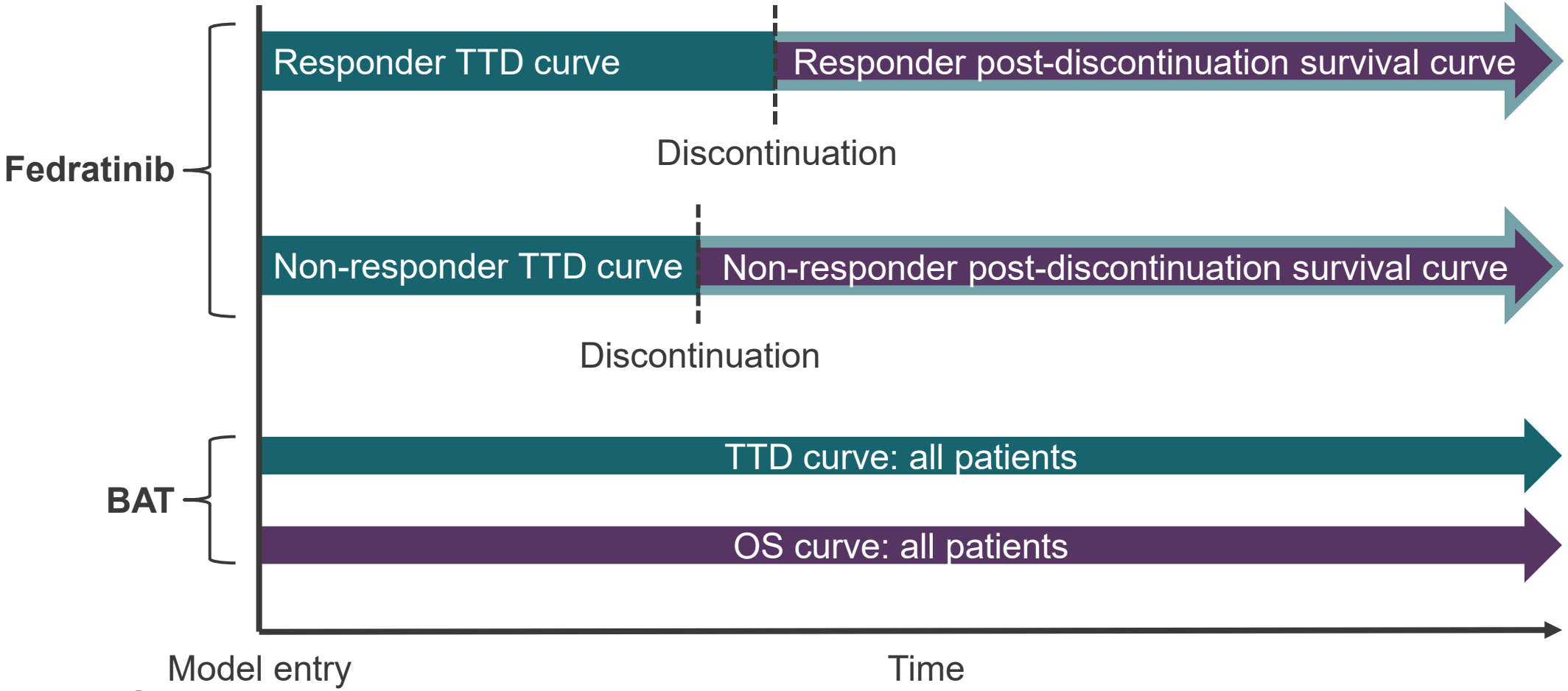
Active treatment state End of life state

BAT, best available therapy; TTD, time-to-treatment discontinuation; OS, overall survival

Company's model: TTD & survival modelling

Company models TTD and survival differently for fedratinib and BAT:

- **Fedratinib:** TTD curves estimated from model entry, split by responders and non-responders at 24 weeks. Survival estimated from discontinuation, split by responders and non-responders at 24 weeks
- **BAT:** TTD and OS curves independently estimated from model entry applied to all patients



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BAT, best available therapy; TTD, time-to-treatment discontinuation; OS, overall survival

BAT evidence sources in the model

Source	Use in model (company base case)	ERG comments
SIMPLIFY-2 *(RCT momelotinib vs BAT, n=52 on BAT)*	• MAIC for spleen or symptom response • BAT composition • AE frequency for BAT as comparator	• Differences in populations between JAKARTA-2 and SIMPLIFY-2 • BAT evidence source most like population entering economic model. Most appropriate evidence source for BAT OS
COMFORT-2 *(RCT ruxolitinib vs BAT, n=73 on BAT, JAKi-naïve)*	• AE frequency for BAT after fedratinib • AML rate for BAT	• Most appropriate data source for AML transformation rate for both BAT and fedratinib arms (longer follow up than JAKARTA-2)
HMRN 2020 *(observational, n=[redacted] second-line treatment)*	• BAT time-to discontinuation	• Concerns about reliability of data, as TTD is above OS (not plausible)
Schain et al. *(observational Norway/Sweden, n=71 discontinued ruxolitinib)*	• BAT overall survival	• Patients discontinued ruxolitinib, different than model population (in which most continue having ruxolitinib) • No patients from UK, may not reflect NHS

ERG

- Company does not use data sources consistently
- Mixing evidence from different studies/populations is not appropriate

AE, adverse event; RCT, randomised controlled trial; MAIC, matching-adjusted indirect comparison; BAT, best available therapy; AML, acute myeloid leukaemia; MF, myelofibrosis; HMRN, Haematological Malignancy Research Network; TTD, time-to-treatment discontinuation; OS, overall survival

Company's model justification and ERG critique

Company

- Discrete event simulation model is similar to that in TA386. It is has advantages in terms of flexibility to model: response assessment; the progressive nature; worsening quality of life within a health state; alternative structural assumptions

ERG

- Model is overly complicated because of individual-based approach and choice to separate patients by response status despite limited evidence
- A simpler approach like a cohort partitioned survival model could have been sufficient
- Key issues:
  - Company model fedratinib and BAT arms differently
  - Choice of fedratinib TTD curves very uncertain due to short trial, clinical hold and censoring
  - Post-treatment discontinuation survival Kaplan-Meier curve for fedratinib responders is based on [redacted], with [redacted]. Survival difference could be because of different approaches for fedratinib and BAT
  - Supportive care health state has not been implemented appropriately – patients spend too long in health state compared to predictions of ERG's clinical experts
  - Large variations in life year predictions between deterministic and probabilistic analyses suggest uncertainty

Is the company model suitable for decision making?

BAT, best available therapy; TTD, time-to-treatment discontinuation

Key unresolved issues

Model driver | Unknown impact | Small impact

Issue	Impact on ICER	Resolved
1. Survival modelling and fedratinib survival benefit (ERG issue 7)		
a. What source of evidence should be used to model BAT OS? b. Is there a survival benefit for fedratinib?		
2. Fedratinib TTD curve (ERG issue 4)		
What is the most appropriate TTD curve for fedratinib?		
3. Subsequent treatment (ERG issue 6)		
What treatment should be modelled after fedratinib?		
4. Ruxolitinib costs (ERG issue 9)		
What costs should be used for ruxolitinib? Should wastage be included?		
5. AML transformation (ERG addendum issue)		
How should the transformation rate to AML be modelled?		

Unresolved issue for committee discussion

AML, acute myeloid leukaemia, BAT, best available therapy; MAIC, matching-adjusted indirect comparison; OS, overall survival; TTD, time-to-treatment discontinuation

Other areas of uncertainty

Model driver | Unknown impact | Small impact

Issue	Summary of issue	Impact	Resolved
Fedratinib dose intensity	• ERG considers a dose intensity after relapse of [redacted]% more plausible (vs. [redacted]% for company)	Small impact	Unresolved
Fedratinib non-responder utilities	• ERG: unclear why non-responder utility using CHMP response definition less than original value • Company: new analyses not directly comparable	Unknown impact	Partially resolved
BAT non-responder utilities	• Company: assume BAT non-responders have no increment utility (based on SIMPLIFY-2) • ERG: generally satisfied, with some uncertainty	Unknown impact	Resolved
Adverse events (AEs)	• ERG prefers AE rates from ITT population (more patients than intermediate-2/high-risk subgroup)	Small impact	Unresolved
Gender in utility regressions	• ERG prefers gender is excluded from regressions if known not to be predictive	Small impact	Unresolved
Stopping rule	• Not in company or ERG base cases. ERG not convinced it would apply, as no other tx options • A stopping rule was accepted in TA386, but this was in the ruxolitinib marketing authorisation	Model driver	Partially resolved

NICE Resolved | Partially resolved/for brief discussion | Unresolved, for discussion

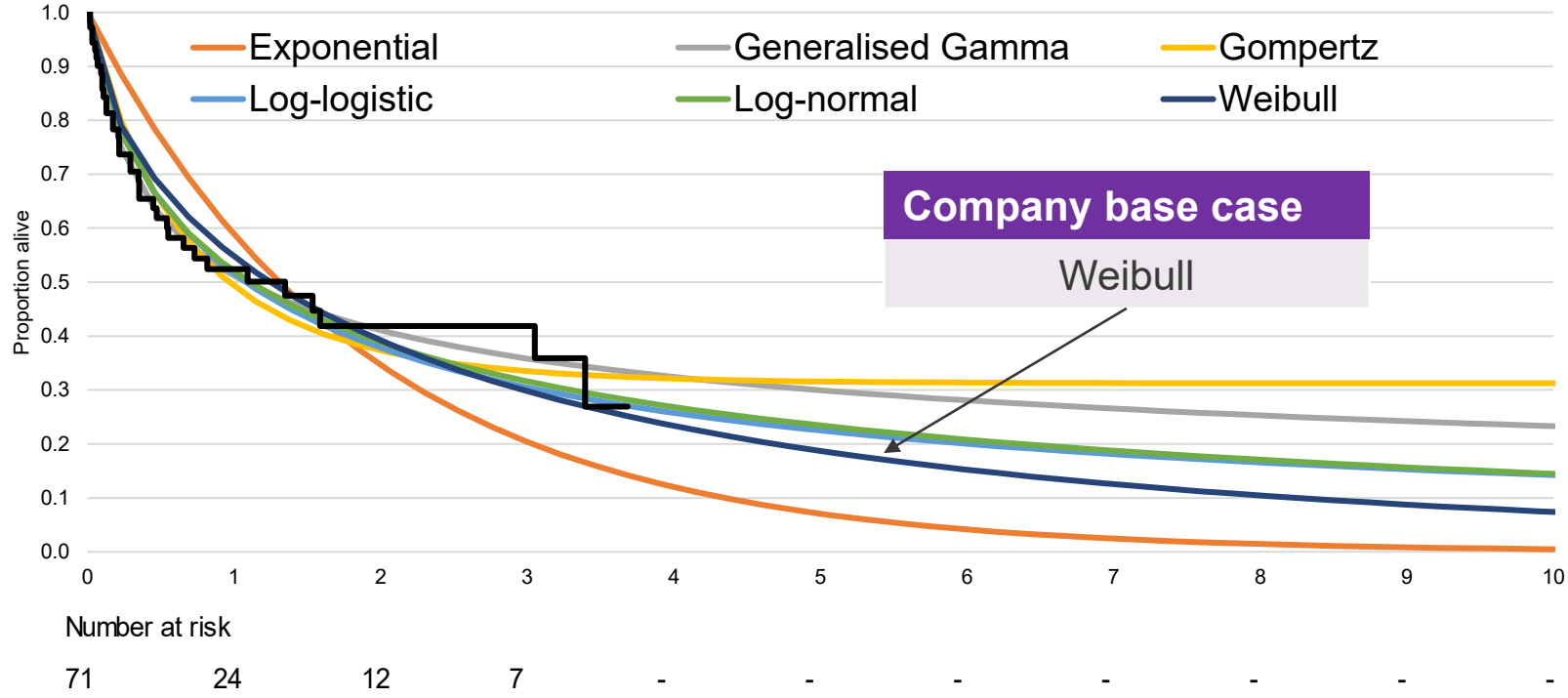
BAT, best available therapy; CHMP; Committee for Medicinal Products for Human Use; ITT, intent to treat; Tx, treatment

Issue 1a: BAT OS, company base case

Company

- Systematic literature review identified 13 studies (2 post review). Updated model includes 7 potential evidence sources for BAT overall survival
- Base case uses Schain et al. 2019 to estimate BAT survival from model entry
  - 71 people with myelofibrosis who discontinued ruxolitinib in Norway and Sweden
  - Advisory board of 7 clinicians indicated this population was most representative of people who could have fedratinib in UK practice
  - Clinicians identified exponential and Weibull distributions as most representative of UK patients. Weibull selected as it best fit the data

Parametric curves fitted to overall survival data from Schain et al., 2019



BAT, best available therapy; OS, overall survival

Issue 1a: BAT OS, company base case

Company

- Composition of BAT in Schain inappropriate for modelling UK costs, but is most representative of those expected to have fedratinib in the UK
- Any OS benefit from ruxolitinib would not be significant – supported by chart review showing that ruxolitinib did not extend OS for patients who continued it after progression

Clinical experts

- Current practice for people R/R to ruxolitinib: 5- and 10-year survival of <5%
- People R/R to ruxolitinib who have stopped ruxolitinib would have worse survival outcomes than those staying on ruxolitinib

ERG

- Using the data from Schain to model OS is not appropriate because:
  - Schain does not reflect modelled population (where most continue ruxolitinib). Schain OS data is from after ruxolitinib is stopped (later in treatment pathway than in model)
  - Concerns comparing OS from observational Schain with JAKARTA-2 which had inclusion criterion of at least 6 month life expectancy
  - Schain had more patients with primary MF and were older (worse OS) than JAKARTA-2
  - Concerns about using survival data from a source when the treatments are not considered reflective of current practice
- Company use SIMPLIFY-2 for BAT response/composition; for consistency, should also use for BAT OS

BAT, best available therapy; MF, myelofibrosis; OS, overall survival; R/R, relapsed/refractory

Issue 1a: BAT OS, other sources of evidence

Company

- Identified 6 additional data sources for BAT overall survival in the model (base case remains Schain et al. 2019)
  - Included an RCT and 5 observational studies. Populations varied by % of patients with intermediate-1 disease, and % having ruxolitinib
- Considered that fedratinib demonstrated survival benefit vs. all data sources

ERG

- Does not consider the other identified studies to be more robust or appropriate
  - Some studies were conducted post-ruxolitinib discontinuation (people may be further along the treatment pathway than people entering the model)
  - Some studies included people with intermediate-1 disease (which is different than the modelled population)
  - Inappropriate to compare OS from observational studies with OS from JAKARTA-2 which had ≥6 month life expectancy
- SIMPLIFY-2 is most appropriate evidence source for BAT; requested survival MAIC with JAKARTA-2 and SIMPLIFY-2

What source of evidence should be used to model BAT OS?

BAT, best available therapy; OS, overall survival; RCT, randomised controlled trial; MAIC, matching-adjusted indirect comparison

Issue 1b: Fedratinib post-discontinuation survival

[redacted]

[redacted]

Company

- Expert opinion indicated it was clinically plausible that responders would have better survival than non-responders
- Non-responders: Weibull, exponential and Gompertz extrapolations seemed reasonable
- Responders: Weibull selected because the expected hazard would initially be relatively low and then increase over time
  - Weibull provided most conservative estimate of survival

ERG

- Estimating time to death following discontinuation separated by response status increases uncertainty
- Kaplan-Meier curve for responders is based on [redacted] where only [redacted] was observed

Issue 1b: Fedratinib response and survival

Company

- Recognises uncertainty with single-arm study
- Noted some evidence of an association between spleen response and survival. Suggests fedratinib improves overall survival, as it had a higher spleen/symptom response than BAT in the MAIC

Clinical experts

- Spleen response (reduction in spleen volume) and to a lesser extent symptom response can be useful surrogates for longer term survival
- Given these were incrementally improved with fedratinib, the assumption of a survival difference is reasonable

ERG

Considers that evidence is suggestive that spleen response could be associated with an improvement in survival but:

- the magnitude of benefit is inconsistent between studies and is highly uncertain
- the relationship has been assessed in people treated with ruxolitinib in first-line only, it is unknown whether the same relationship would apply following ruxolitinib failure

BAT, best available therapy; MAIC, matching-adjusted indirect comparison

Issue 1b: FED vs BAT survival, MAIC using SIMPLIFY-2

Company

- SIMPLIFY-2 OS data not reliable:
  - source's slides and some results did not match Kaplan-Meier curve
  - based on post-hoc analyses
  - cross-over allowed after 24 weeks
- Small number of transfusion-dependent patients in JAKARTA-2 have large impact

ERG

- After matching, fedratinib OS similar to BAT OS from SIMPLIFY-2 but, could be worse after adjusting for important variables such as platelet count and transfusion dependence (see below)
- Prefer SIMPLIFY-2 OS up to 24 weeks before cross-over (no OS benefit)

MAIC results: Fedratinib vs BAT, depending on prognostic factors matched

Prognostic factors	HR (95% CI)
None (naïve)	[redacted]
Risk category*	[redacted]
Risk category*, age and haemoglobin	[redacted]
Risk category*, age, haemoglobin, transfusion dependence, platelet counts	[redacted]

[redacted]

* intermediate-2 or high-risk disease based on DIPSS

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FED, fedratinib; BAT, best available therapy; MAIC, matching-adjusted indirect comparison; DIPSS, Dynamic International Prognostic Scoring System; HR, hazard ratio; OS, overall survival;

Issue 1b: Assumption of survival difference

Company

- Base case: naïve comparison using intermediate-2 or high-risk subgroup from JAKARTA-2 for fedratinib, and BAT from Schain et al. 2019
  - Undiscounted model years: BAT, 2.394 and fedratinib, 2.912 (difference 0.518)
- Parametric models based on clinical expert advice and advisory board meeting
- JAKARTA results support a fedratinib survival benefit compared with placebo in people who had no previous treatment with JAK2 inhibitors (OS HR [redacted], 95% CI [redacted] to [redacted]). Should be interpreted with caution given differences in patient populations

Clinical expert

- Assuming a survival benefit for fedratinib is reasonable

ERG

- Comparison with Schain et al. 2019 is not appropriate
- Model-predicted survival difference because of different modelling approaches rather than difference in response rates
- Comparison of survival from JAKARTA-2 and SIMPLIFY-2 up to week 24 does not support assumption of fedratinib survival advantage
- Exploratory naïve comparison of survival from JAKARTA-2 and COMFORT trials also suggests no survival benefit for fedratinib
- Based on available evidence, no survival difference should be assumed

BAT, best available therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; JAK2, Janus kinase 2

Issue 2: Fedratinib TTD curve

ERG

- Choice of curve uncertain due to short trial, clinical hold and censoring for up-titration
- Other parametric distributions could be plausible. Provided scenario analysis assuming Gompertz distribution for both groups (conservative)
- Selecting a different distribution can have a large (>£10,000/QALY gained) impact on ICER

What is the most plausible TTD curve for fedratinib?

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CHMP, Committee for Medicinal Products for Human Use; TTD, time-to-treatment discontinuation; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Issue 3: Subsequent treatment

Company

- **BAT arm:** People continue to have ruxolitinib after relapse because there are no other treatment options. Supported by clinical advice
- **Fedratinib arm:** People have BAT (without ruxolitinib) after relapse
  - No evidence that fedratinib would be continued after relapse
  - Use clinical advice for assumptions after fedratinib is stopped:
    - [redacted] of non-responders and [redacted] of responders have BAT
    - [redacted] of non-responders and [redacted] of responders have supportive care

Clinical experts

- Expect treatment to continue with fedratinib or if disease worsened or relapsed, most would go back to ruxolitinib or join a clinical trial

ERG

- Inconsistent assumption between BAT and fedratinib
- After relapse, suboptimal fedratinib or re-treat with ruxolitinib is more appropriate than BAT
- Prefer to assume fedratinib is continued suboptimally (similar to ruxolitinib assumption)
- Requested scenarios where people remain on fedratinib or switch to ruxolitinib, company assume 11.5% have no other treatments and thus no drug costs. This does not align with BAT assumptions (which are that people have hydroxyurea, prednisone or prednisolone)

What treatment should be modelled after relapse on fedratinib?

BAT, best available therapy

Issue 4: Ruxolitinib costs

Background

- Ruxolitinib dose varies based on platelet count – estimating its cost is difficult
- Cost from TA386 cannot be used as this was for a different patient population (first-line)
- In TA386, no drug wastage for ruxolitinib was accepted – reflected usage in practice

Company

- Estimated proportion of people with platelet count <100 x 10^9/L in SIMPLIFY-2 (these have a lower dose). Assumed normal distribution, and used mean and standard deviation
  - From this, **39%** have lower platelet count. Recent SIMPLIFY-2 evidence (Gupta et al.) suggests this figure may be lower
- Assume 5% ruxolitinib drug wastage in base case

Clinical expert

- Ruxolitinib is often under-dosed, leading to suboptimal benefit

ERG

- Normal distribution for platelet counts leads to lots of people with values less than zero
- Lognormal distribution more appropriate: **49%** have lower platelet count
- Gupta et al. also state only 5.5% of people had max dose at end of randomised treatment
- Inclusion of drug wastage not appropriate in line with committee decision from TA386

What costs should be used for ruxolitinib? Should wastage be included?

Issue 5: AML transformation rate

Background

- Original company model included AML as a health state. Model has been updated to include AML as an adverse event
- Original model used same AML rate for fedratinib and BAT arms from JAKARTA-2 ITT population ([redacted]) as uncertain if fedratinib treatment influences AML transformation

Company

Updated model uses evidence from COMFORT-2 (4 events) for BAT and evidence from JAKARTA-2 intermediate-2/high-risk population ([redacted]) for fedratinib. Assume [redacted] transformation for fedratinib arm

ERG

- Changes appear arbitrary and without documentation or description and favour fedratinib
- The same AML transformation rate should be used for both arms for consistency
- Evidence from pooled COMFORT trials for ruxolitinib is preferred to inform AML transformation because of longer follow-up and larger number of patients

How should the transformation rate to AML be modelled?

AML, acute myeloid leukaemia; BAT, best available therapy; ITT, intent to treat

End of life (1/2)

Background (TA386 – ruxolitinib for first-line myelofibrosis)

- Median BAT OS of 28 months from COMFORT-2 (intermediate-2 or high-risk disease)
- Median BAT OS estimated at 1.3 to 2.3 years for people with **high-risk disease**
- Not possible to calculate median OS benefit for ruxolitinib from COMFORT-2. Indirect treatment comparison of ruxolitinib arm and DIPSS cohort suggested benefit 1.5 years
- End of life criteria met for people with **high-risk disease**

Company

- Survival outcomes in patients who have had ruxolitinib are poor. Studies indicate median OS of 13–16 months after ruxolitinib. Does not make case for EoL in high-risk disease only
- There would be an expected survival benefit with fedratinib in people who are R/R/I to ruxolitinib: these people would be considered end of life

Clinical experts

- Survival is poor for disease relapsed/refractory to ruxolitinib (18-24 months); indication meets end of life criteria. Expect proportion alive at 5 and 10 years <5%
- All but 1 of patients treated in JAKARTA-2 trial had overall survival less than 3 years

ERG

- Evidence does not suggest a survival difference between fedratinib and BAT
- Not possible to split into intermediate-2 and high-risk groups because of small sample size

BAT, best available therapy; OS, overall survival; DIPSS, Dynamic International Prognostic Scoring System; EoL, end of life; R/R/I, relapsed/refractory/intolerant

End of life (2/2)

Median OS data after ruxolitinib discontinuation from different data sources

Data source	Fedratinib	BAT
JAKARTA-2	Not reached ([redacted] alive at 12 months)	N/A
Schain 2019	N/A	16 months
HMRN 2020	N/A	[redacted] months
COMFORT-2	N/A	16 months

Life expectancy from model (months)

Life expectancy	Intervention	Company base case	ERG base case 1	ERG base case 2
Mean life expectancy (months)	Fedratinib	34.9	34.9	34.9
	BAT	28.7	34.9	34.9
	Incremental	6.2	0.0	0.0
Median life expectancy (months)	Fedratinib	[redacted]	[redacted]	[redacted]
	BAT	[redacted]	[redacted]	[redacted]
	Incremental	[redacted]	0.0	0.0

Have the end of life criteria been met?

BAT, best available therapy; OS, overall survival

Other considerations

Innovation

- Clinical experts: Yes in that there is currently no approved therapy to be used after failure of ruxolitinib, but not particularly innovative as a new class of JAK2 inhibitor
- Company: Fedratinib is a potential novel treatment option
- MPN Voice: Yes, if the data is robust then this technology is a step change
- Comparator company: No, fedratinib is not to be considered to be innovative; it is the second licensed JAK-inhibitor class treatment

Equality issues

- No equalities issues raised that can be addressed in a technology appraisal. See EIA for more information (updated after committee discussion)

JAK, Janus kinase

Differences between company, ERG base cases

Assumption	Company	ERG
Survival difference	Yes	No
Post-fedratinib treatment	BAT without ruxolitinib (mostly hydroxyurea) and/or supportive care	**Base case 1:** Fedratinib* until supportive care **Base case 2:** Ruxolitinib* until supportive care
BAT drug costs for patients after fedratinib (in ERG base cases)	Exclude BAT drug costs for those not on JAKis	Include BAT drug costs for those not on JAKis
Gender in utility regressions	Included	Excluded
Ruxolitinib wastage	Included 5% wastage	Excluded
Suboptimal fedratinib dose intensity (in ERG base cases)	[redacted]	[redacted]
AML transformation rate	**BAT:** COMFORT-2 **Fedratinib:** JAKARTA-2 intermediate-2/high-risk population ([redacted])	Same rate between arms (from COMFORT-2)
Fedratinib adverse event rates	JAKARTA-2 intermediate-2/high-risk population (n=81)	JAKARTA-2 ITT population (n=97)

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* 88.5% of patients; BAT, best available therapy; JAKi, Janus kinase inhibitor; AML, acute myeloid leukaemia; AE, adverse event; ITT, intent to treat

Company's cost-effectiveness results (FED PAS, RUX list price)

	Total			Incremental			
Technologies	Costs (£)	Life years	QALYs	Costs (£)	Life years	QALYs	ICER incremental (£/QALY)
Deterministic							
BAT	[redacted]	2.394	1.357	-	-	-	-
Fedratinib	[redacted]	2.912	1.836	11,866	0.518	0.479	**24,784**
Probabilistic							
BAT	[redacted]	3.085	1.445	-	-	-	-
Fedratinib	[redacted]	3.983	2.122	19,219	0.897	0.676	**28,418**

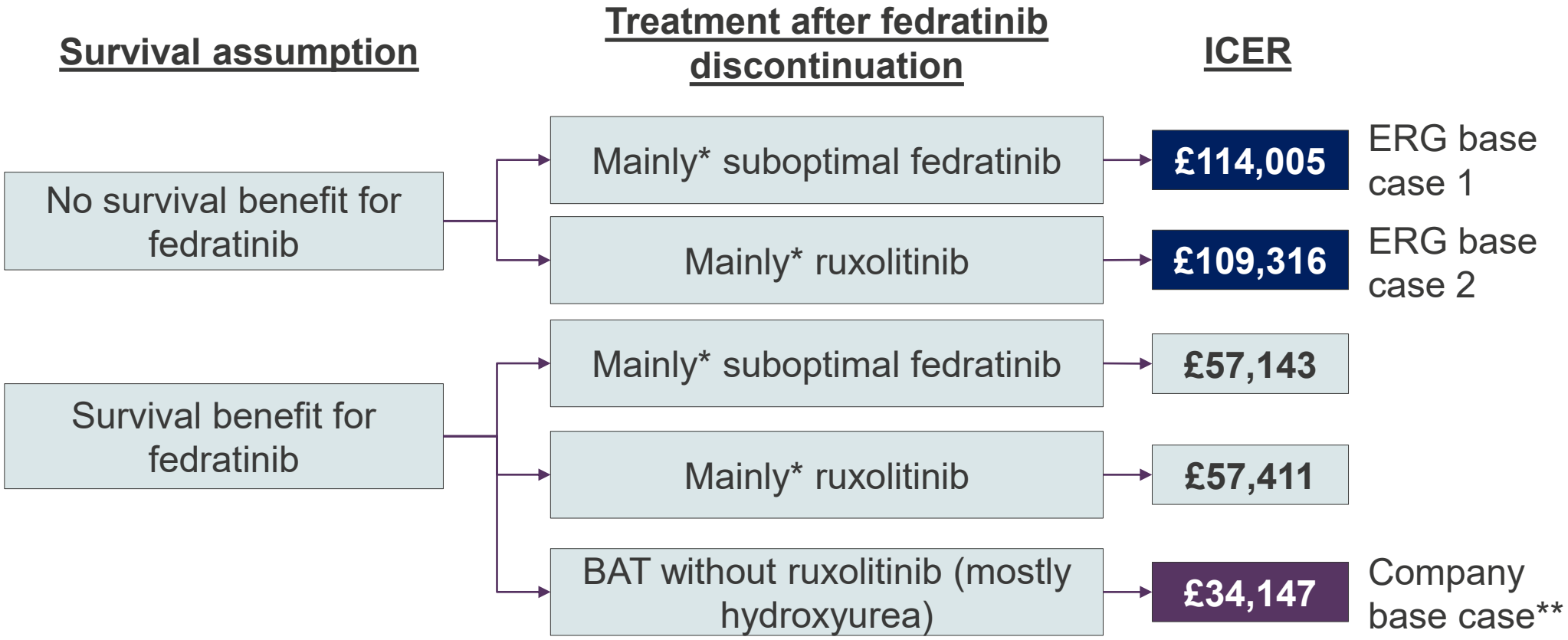
ERG

- Reiterates the company's base-case assumptions are not appropriate
- Results should be interpreted with considerable caution as different approaches to discontinuation are used between arms

Cost effectiveness results with confidential commercial agreement for ruxolitinib will be considered in part 2

BAT, best available therapy; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

ERG cost-effectiveness scenarios (FED PAS, RUX list price)



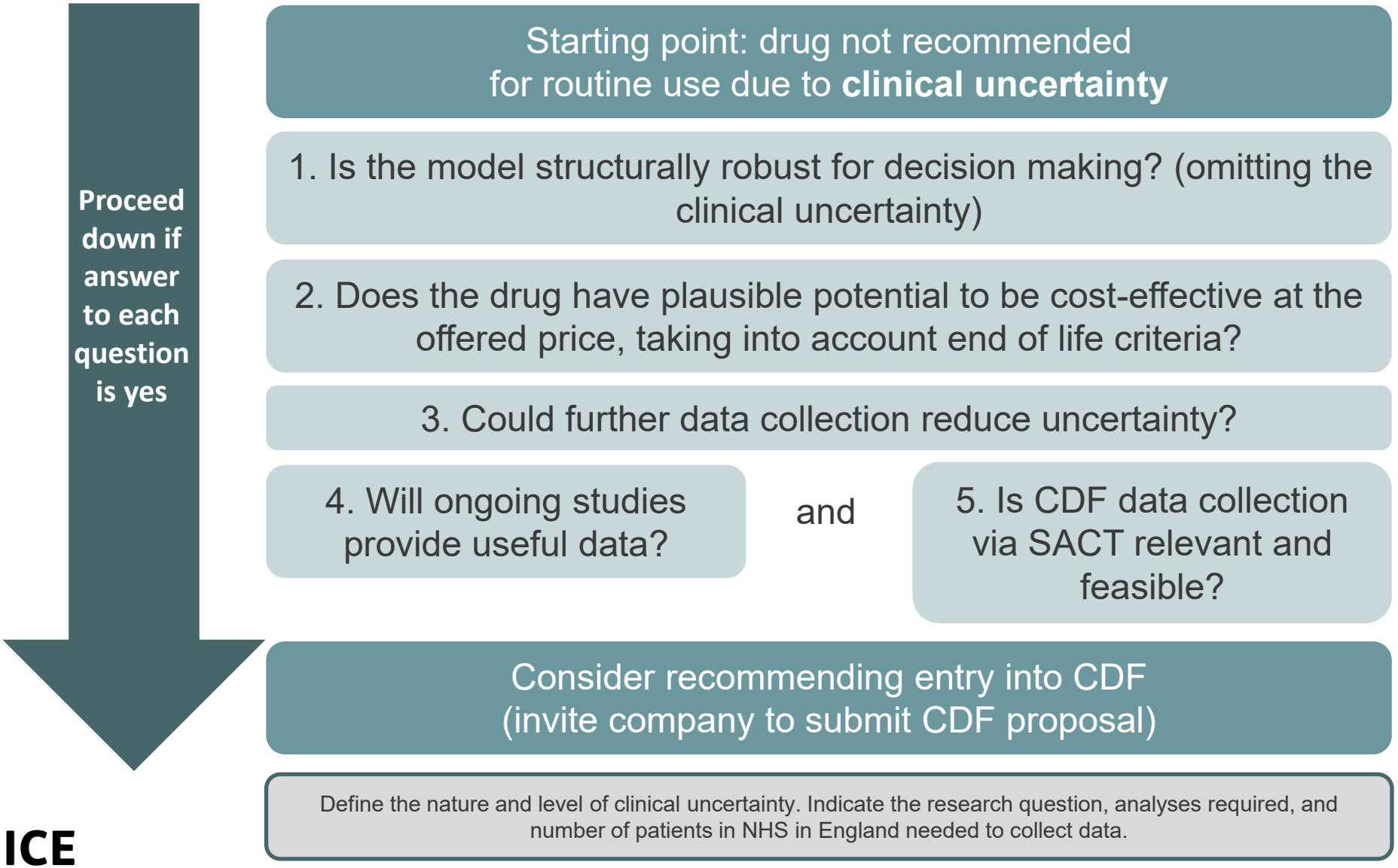
All ICERs include other ERG-preferred assumptions: BAT drug costs included after fedratinib for those not having JAKis; gender excluded from utility regressions; ruxolitinib wastage excluded; sub-optimal fedratinib dose intensity of [redacted]; same AML transformation rate between arms from COMFORT-2; fedratinib adverse event rate based on JAKARTA-2 ITT population

*88.5% of patients; ** with other ERG-preferred assumptions.

FED, fedratinib; PAS, patient access scheme; RUX, ruxolitinib; ICER, incremental cost-effectiveness ratio; BAT, best available therapy; JAKi, Janus kinase inhibitor; AML, acute myeloid leukaemia; ITT, intent to treat

Cancer Drugs Fund (1/2)

Committee decision making: CDF recommendation criteria



FREEDOM-2: phase 3, randomised study

Population (n=192)	Adults with primary, post-PV or post-ET myelofibrosis with splenomegaly • ECOG PS 0, 1 or 2 • DIPSS risk score of intermediate-2 or high • Previously treated with ruxolitinib
Locations	112 including 7 UK sites
Intervention	Fedratinib (400 mg/day)
Comparator	Best available therapy (BAT)
Follow up	For primary outcome 6 cycles (about 6 months), for overall survival about [redacted] months
Primary outcome	Proportion of subjects with ≥35% spleen volume reduction
Secondary outcomes	• Proportion of subjects with ≥50% reduction in total symptom score • Proportion of subjects with ≥25% reduction in spleen volume • Duration of ≥50% reduction in spleen size by palpation • Duration of ≥50% reduction in total symptom score • Time from randomisation to death (any cause) or disease progression • Health-related quality of life • Overall survival
Expected completion	• Primary completion [redacted]

NICE

Post-PV, post-polycythaemia vera; Post-ET, post-essential thrombocythemia; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status

Cancer Drugs Fund (2/2)

Remaining uncertainty	Company comments: how uncertainty can be addressed
JAKARTA-2 generalisability	FREEDOM-2 is a phase 3 RCT with 7 UK locations
Indirect treatment comparison	FREEDOM-2 compares fedratinib directly with BAT
Comparator for R/R disease vs. intolerance	FREEDOM-2 and CDF data could provide evidence for treatment differences between populations
Model structure, OS modelling and fedratinib survival benefit	Mature FREEDOM-2 data (24 months follow-up) could inform model and provide evidence for survival benefit
Fedratinib TTD curve, stopping rule and subsequent treatment	CDF data could provide evidence for treatment discontinuation and subsequent treatment in practice
AML transformation rates	FREEDOM-2 could inform these
Dose intensity	CDF data could provide evidence for dose intensity for those who remain on suboptimal fedratinib
Ruxolitinib costs	FREEDOM-2 could inform ruxolitinib costs and wastage

ERG
FREEDOM-2 may not resolve long-term survival uncertainty as people randomised to BAT can crossover to fedratinib after cycle 6 (or before with splenomegaly progression)

NICE

Should fedratinib be entered into the CDF?

RCT, randomised controlled trial; BAT, best available therapy; R/R, relapsed or refractory; OS, overall survival; TTD, time-to-discontinuation

Back up slides

BAT evidence sources: characteristics and composition

Large differences in % of people having ruxolitinib between BAT sources

	JAKARTA-2 (ITT)	SIMPLIFY-2	HMRN 2020	Schain et al.
Baseline characteristics				
Median age	67	69	[redacted]	64
Intermediate-2	48%	54%	Not reported	Not available
High-risk	35%	15%		
ECOG PS 0	27%	37%		
ECOG PS 1	46%	50%		
ECOG PS 2	24%	14%		
Transf.-dependent	14%	37%		
BAT composition				
Anagrelide	Not applicable	0% (NR)	[redacted]	0%
Busulfan		0% (NR)	[redacted]	8%
Danazol		0% (NR)	[redacted]	5%
Hydroxyurea		23%	[redacted]	32%
Interferon alfa		0% (NR)	[redacted]	0%
PEG-IFN-a 2a		0% (NR)	[redacted]	5%
Prednis(ol)one		6%	[redacted]	32%
Thalidomide		0% (NR)	[redacted]	5%
Ruxolitinib		89%	[redacted]	0%

COMFORT-2	
Baseline characteristics	
Not available for population who had discontinued ruxolitinib	
BAT composition (TA386)	
33%	Observation alone
47%	Hydroxyurea
16%	Glucocorticoids
7%	Epoetin-alpha
7%	Immune modulators
6%	Purine*
4%	Androgens
4%	Interferons
3%	Nitrogen mustard*
3%	Pyrimidine*

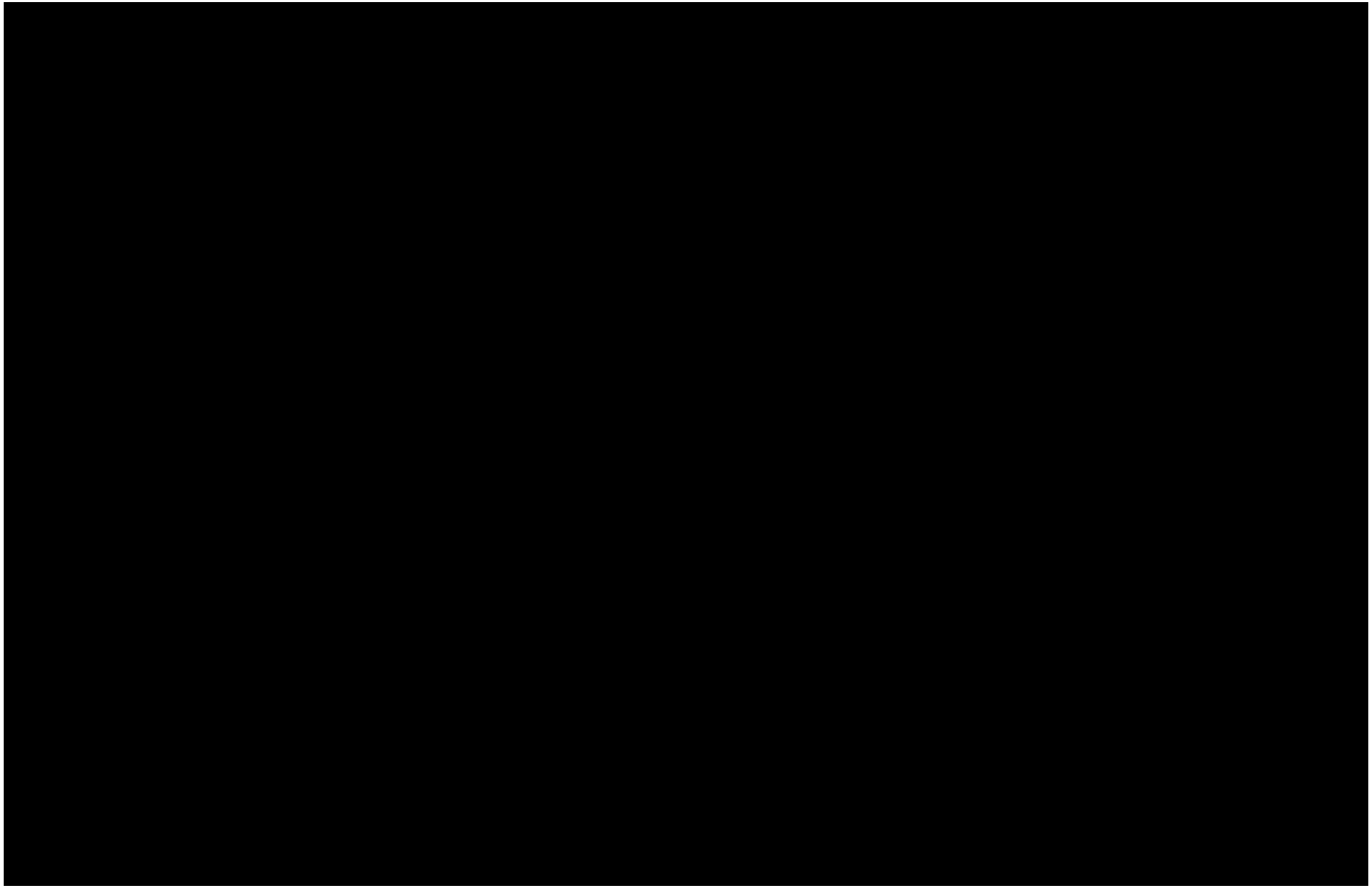
HMRN, Haematological Malignancy Research Network; ECOG PS, Eastern Cooperative Oncology Group performance status

*analogues

Evidence for BAT: SIMPLIFY-2, phase 3 RCT

Population (BAT n=52)	• Primary MF, post-polycythaemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis • Intermediate-1 (symptomatic), intermediate-2, or high risk myelofibrosis (DIPSS) • Currently or previously treated with ruxolitinib (≥28 days unless intolerant) • There was no inclusion/exclusion criteria for platelet count at baseline	
Locations	52 study centres in 8 countries (4 in the UK)	
Characteristics	• Disease type • Risk status • ECOG • Median age • Male	Primary MF: 57.7%, Post-PV: 23.1%, Post-ET 19.2% Intermediate-2: 53.8%, high: 15.4% PS 0: 36.5%, PS 1: 50.0%, PS 2: 13.5% 69.4 years 46.2%
Intervention	Momelotinib	
Comparator	BAT (ruxolitinib 88.5%)	
Outcomes	Proportion of subjects with ≥35% reduction in spleen volume at week 24	

Overall survival model output



Dose intensity post fedratinib

Background

- Relative dose intensity for fedratinib included in model to capture impact of dose reductions or missed doses
- Dose intensity of [redacted]% to adjust for up-titration

Company

- Provided scenario analysis assuming patients continue to have fedratinib after relapse using the same proportion of patients having ruxolitinib as in the BAT arm
- Used dose intensity of [redacted]% for patients having fedratinib after relapse
  - Value calculated from the dose intensity in the subset of patients who did not get up-titrated

ERG

- Removing up-titrated patients (rather than capping maximum dose at 400mg) is arbitrary and not appropriate
- A dose intensity of [redacted]% is more plausible for patients maintained on fedratinib

NICE

What dose intensity should be assumed for people continued on sub-optimal fedratinib?

BAT, best available therapy

Stopping rule

Background

- In TA386 a 24-week stopping rule accepted in line with ruxolitinib marketing authorisation: "treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy"
- Fedratinib marketing authorisation does not include stopping rule: "treatment may be continued for as long as patients derive clinical benefit"

Company

- Base case does not include stopping rule. Non-responders to fedratinib discontinue treatment based on TTD curves
- Stopping rule included as a scenario, in which non-responders immediately switch to BAT
- In model updated after technical engagement, stopping rule impacts OS which addresses an initial ERG concern

Clinical experts

- Challenging to validate stopping rule. Would expect people with disease relapse on fedratinib to remain on it unless there are other treatment options available

ERG

- Generally agrees that new model structure allows it to better capture any potential impact associated with a stopping rule
- Stopping rule could in theory apply to other JAK inhibitors in practice
- Unclear if it would apply to this subgroup after ruxolitinib with no other treatment options

NICE

Is a 6-month stopping rule appropriate?

TTD, time-to-treatment discontinuation; BAT, best available therapy; OS, overall survival; JAK, Janus kinase

ERG updates to company base case (FED PAS, RUX list price)

Deterministic results	Assumes survival difference and patients discontinue fedratinib early		
Incremental results:	Costs (£)	QALYs	ICER
Company analysis	[redacted]	[redacted]	**24,736**
1. Remove gender in utility regressions	[redacted]	[redacted]	25,061
2. Remove ruxolitinib wastage	[redacted]	[redacted]	29,095
3. Same AML rate (COMFORT-2)	[redacted]	[redacted]	29,243
4. Adverse event rate from ITT population	[redacted]	[redacted]	29,776
ERG correction (1-4)	[redacted]	[redacted]	**34,147**
ERG assumptions + Gompertz TTD (curves cross at 3.5 years)	[redacted]	[redacted]	20,160

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BAT, best available therapy; FED, fedratinib; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; RUX, ruxolitinib, TTD: time-to-treatment discontinuation

ERG base cases (FED PAS, RUX list price)

Deterministic results	ERG base case 1: No survival difference, people remain on FED after relapse			ERG base case 2: No survival difference, people switch to RUX after FED		
Incremental results:	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Company analysis	[redacted]	[redacted]	**61,513**	[redacted]	[redacted]	**67,173**
1. Inclusion non-JAKi costs	[redacted]	[redacted]	61,589	[redacted]	[redacted]	67,249
2. Utility regression: gender excluded	[redacted]	[redacted]	63,187	[redacted]	[redacted]	69,001
3. No wastage for ruxolitinib	[redacted]	[redacted]	81,997	[redacted]	[redacted]	82,987
4. Dose intensity after fedratinib ([redacted]%)	[redacted]	[redacted]	66,833	[redacted]	[redacted]	67,173
5. Same AML rate (COMFORT-2)	[redacted]	[redacted]	83,247	[redacted]	[redacted]	89,189
6. Adverse event rate from ITT population	[redacted]	[redacted]	61,767	[redacted]	[redacted]	67,443
ERG assumptions (1-6)	[redacted]	[redacted]	**114,005**	[redacted]	[redacted]	**109,316**
ERG assumptions + Gompertz TTD	[redacted]	[redacted]	127,846	[redacted]	[redacted]	121,392

NICE

FED, fedratinib; PAS, patient access scheme; RUX, ruxolitinib; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; BAT, best available therapy; JAKi, Janus kinase inhibitor; AML, acute myeloid leukaemia; ITT, intent to treat; TTD, time-to-treatment discontinuation