Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis (CDF review of TA756) [ID5115]

Part 1: redacted for screen

Technology Appraisal Committee B (14th August 2024)

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Company: Bristol-Myers Squibb

Fedratinib for treating disease-related splenomegaly or symptoms in myelofibrosis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Summary of original appraisal (TA756) and CDF Review

- OS for fedratinib compared with BAT uncertain
- Model overly complex
- Inconsistent modelling assumptions and use of evidence

TA756: Recommended for use in CDF (key uncertainties):

- whether fedratinib extends OS compared to BAT
- uncertain OS for those on BAT

Review of TA756

- FREEDOM-2 data cut off December 2022
- SACT data cut off October 2022
- SACT OS: reassessment of vital status February 2024

Abbreviations: BAT, best available therapy, CDF, Cancer Drugs Fund; OS, overall survival; SACT, systemic anti-cancer therapy

Key issues

Issues for committee discussion			ICER impact
Decision problem	1	No comparison against momelotinib	Unknown
Clinical evidence	2	High proportion of people crossing over from BAT to fedratinib in FREEDOM-2: company assumes TTD and OS are the same for fedratinib and BAT	Large
Cost-effectiveness	3	Composition of BAT after fedratinib: whether includes suboptimal fedratinib	Large
	4	Proportion of people transitioning to supportive care after fedratinib	Large
	5	Utility gains for no response to fedratinib and BAT	Large
	6	Costing of ruxolitinib assumes high wastage due to dose changes	Large
	7	Duration of suboptimal ruxolitinib within BAT	Large
	8	Estimates of OS and TTD from FREEDOM-2 overestimate ToT and OS compared with SACT – which data source should be used?	Large
Other issues		• Definition of spleen volume response and symptom response	Small
		• Red blood cell transfusion & sex-specific utilities modelling	Small

Abbreviations: BAT, best available therapy, OS, overall survival; SACT, systemic anti-cancer therapy; ToT, time on treatment; TTD, time to treatment discontinuation

Background on myelofibrosis

Classification and epidemiology

- Bone marrow cancer in which the marrow is replaced by scar (fibrous) tissue
- Occurs more often as people get older, with average age of diagnosis being around 65 years
- 10-year prevalence of 3.2 per 100,000 and an annual incidence of 0.6 per 100,000 in the UK. 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)

Symptoms and prognosis

- Spleen enlargement (splenomegaly) may cause abdominal pain, dyspnoea (shortness of breath), early satiety (feeling full) and faecal incontinence, along with progressive anaemia
- To guide treatment, myelofibrosis is classified into low-, intermediate- and high-risk categories according to the Dynamic International Prognostic Scoring System (DIPSS)
- People with relapsed and refractory disease have reduced life expectancy with median survival of 13-16 months post-ruxolitinib

Patient perspectives

Submissions from MPN voice and Leukaemia Care

Living with myelofibrosis

- Debilitating chronic condition that has a major impact on quality of life, with significant negative social and economic impacts on individuals with disease and their carers. Symptoms include:
  - cytopenia, fatigue, pain, early satiety, portal hypertension pruritis, night sweats, fever and cachexia

Unmet need

- Only cure is stem cell transplant but most people with MF are not eligible
- Non-targeted treatments such as hydroxycarbamide and interferon have limited effectiveness
- Response to targeted therapies (ruxolitinib) wanes over time and prognosis for relapsed or refractory disease is very poor

Fedratinib

- Provides better control of symptoms such as fatigue, night sweats, bone pain and severe itching
- For 3 individuals splenomegaly reduced significantly after treatment with fedratinib
- Well tolerated and may cause some initial side effects after the first dose

"My concern is that for 50 percent of patients, ruxolitinib stops working after two to three years - there isn't yet a viable follow-on medication"

"I get tired easily and have had to retire on ill health grounds from working as GP due to fatigue/struggling cognitively"

"Extreme fatigue and bone pain make it impossible on some days to stand and cook, walk dog, play with kids, socialise"

Abbreviations: MF, myelofibrosis; MPN, myeloproliferative neoplasms

Clinical perspectives

Aim of treatment

- Multiple aims depend upon the age and disease status of the person with the disease. These include improving quality of life, reducing the impact of disease-associated symptoms, mitigating erythropoietic injections and addressing issues such as sweats, weight loss, itching or bulky spleen

Unmet need/current treatment options

- Will provide an additional treatment option to give clinicians and individuals more choices
- Need for novel treatment which can alter disease trajectory and improve survival

Fedratinib

- Effective therapy for people with intermediate-2 or high-risk myelofibrosis who need treatment
- At least similar rates of spleen volume reduction compared with both ruxolitinib and momelotinib and at least similar rates of symptomatic improvement as compared with ruxolitinib
- No frequent adverse effects but people may have an increased risk of nausea, vomiting and diarrhoea in initial weeks which can be effectively managed with cyclizine and loperamide

Fedratinib (Increbic, Bristol-Myers Squibb)

Company's population narrower than marketing authorisation

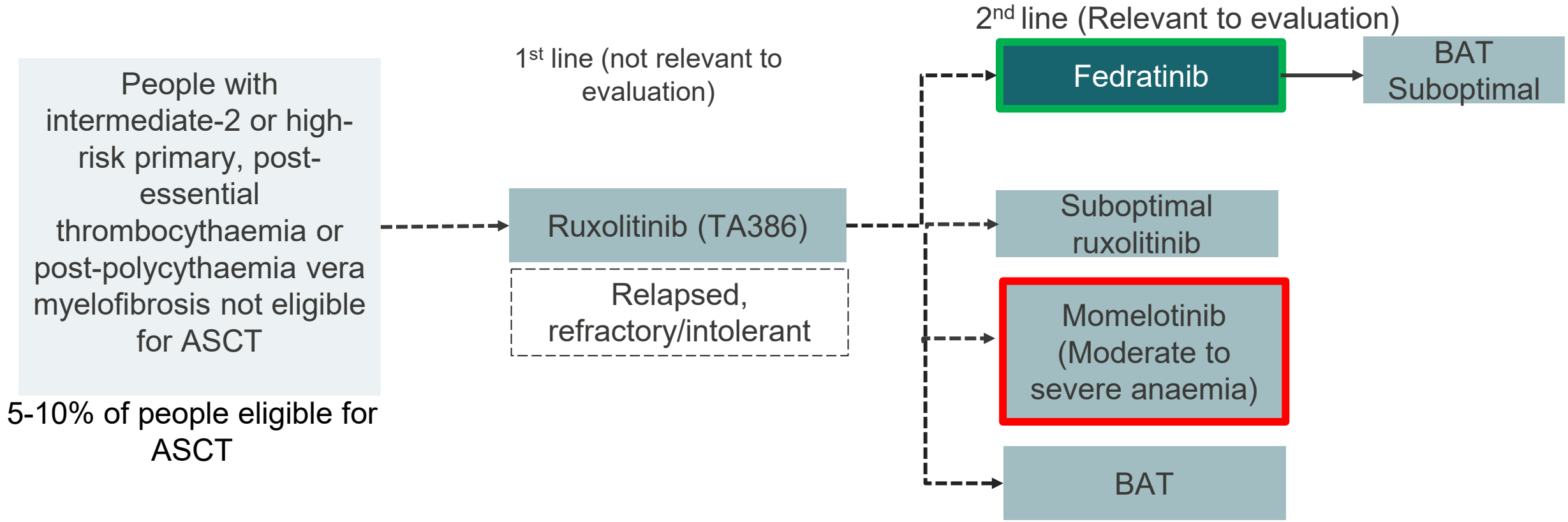
Marketing authorisation	'For the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor-naïve or who have been treated with ruxolitinib.' "Initiating treatment with Inrebic is not recommended in patients with a baseline platelet count below 50 x 109/L and ANC < 1.0 x 109/L."
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 £6,119.68 per pack (120 x 100 mg capsules) • There is a confidential patient access scheme

Abbreviations: ANC, absolute neutrophil count; JAK, Januse Kinase

Treatment pathway: intermediate-2 and high-risk myelofibrosis

TA756: Company positioned fedratinib in people with intermediate-2 or high-risk disease who have had ruxolitinib

Figure: The current NHS intermediate-2 and high-risk myelofibrosis treatment pathway



*BAT includes: Ruxolitinib; hydroxycarbamide, other chemotherapies, androgens, splenectomy; radiation therapy, erythropoietin; RBC transfusion

Is fedratinib positioning reflective of NHS practice?

Proposed position

Not considered comparator

Abbreviations: BAT, best available therapy; ASCT, allogenic stem cell transplant

Key issues: No comparison with momelotinib

Unknown Impact ?

Background
- NICE final scope comparators: established clinical practice and momelotinib (subject to NICE evaluation)
- No comparison provided with momelotinib

Company
- Guidance for momelotinib (TA957) was published in March 2024 and cannot be considered established NHS clinical practice
- Momelotinib recommended in people with severe anaemia: consider the potential overlap between momelotinib and fedratinib eligible population is a very small subgroup

EAG
- FREEDOM-2 baseline Hb ≤100g/L: fedratinib 67% and BAT 61%
- TA957 (momelotinib) considered 2 definitions of moderate anaemia Hb ≤100g/L and Hb ≤120g/L
- National Cancer Institute defines moderate to severe anaemia with Hb ≤100g/L: at least 60% population from FREEDOM-2 had moderate to severe anaemia
- Consider momelotinib a relevant comparator for a substantial population within the company's target population

Is momelotinib a relevant comparator for fedratinib?

NICE Abbreviations: BAT, best available therapy; Hb, Haemoglobin TA, technology appraisal

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Baseline characteristics: FREEDOM-2 & SACT

EAG: baseline characteristics from FREEDOM-2 & SACT broadly similar but had more males
Higher median age in SACT and at least 60% population classed as moderate to severe anaemia at baseline

Characteristic		FREEDOM-2		SACT
		Fedratinib (N=134)	BAT (N=67)	Fedratinib (n=54)
Age, median years (range)		70 (40-86)	68 (38-91)	72 (NR)
Sex	Male	75 (56%)	30 (45%)	41 (76%)
	Female	59 (44%)	37 (55%)	13 (24%)
Risk status	Intermediate-2	102 (76%)	51 (76%)	37 (69%)
	High risk	30 (22%)	16 (24%)	17 (31%)
Hb level	Median (range)	9.3 (5.7-14.4)	9.4 (6.5-14.0)	NR
	≤100 g/L	90 (67%)	41 (61%)	NR
	>100 g/L	44 (33%)	26 (39%)	NR
At least 1 prior anti-cancer therapy other than ruxolitinib		27 (20%)	7 (10%)	NR

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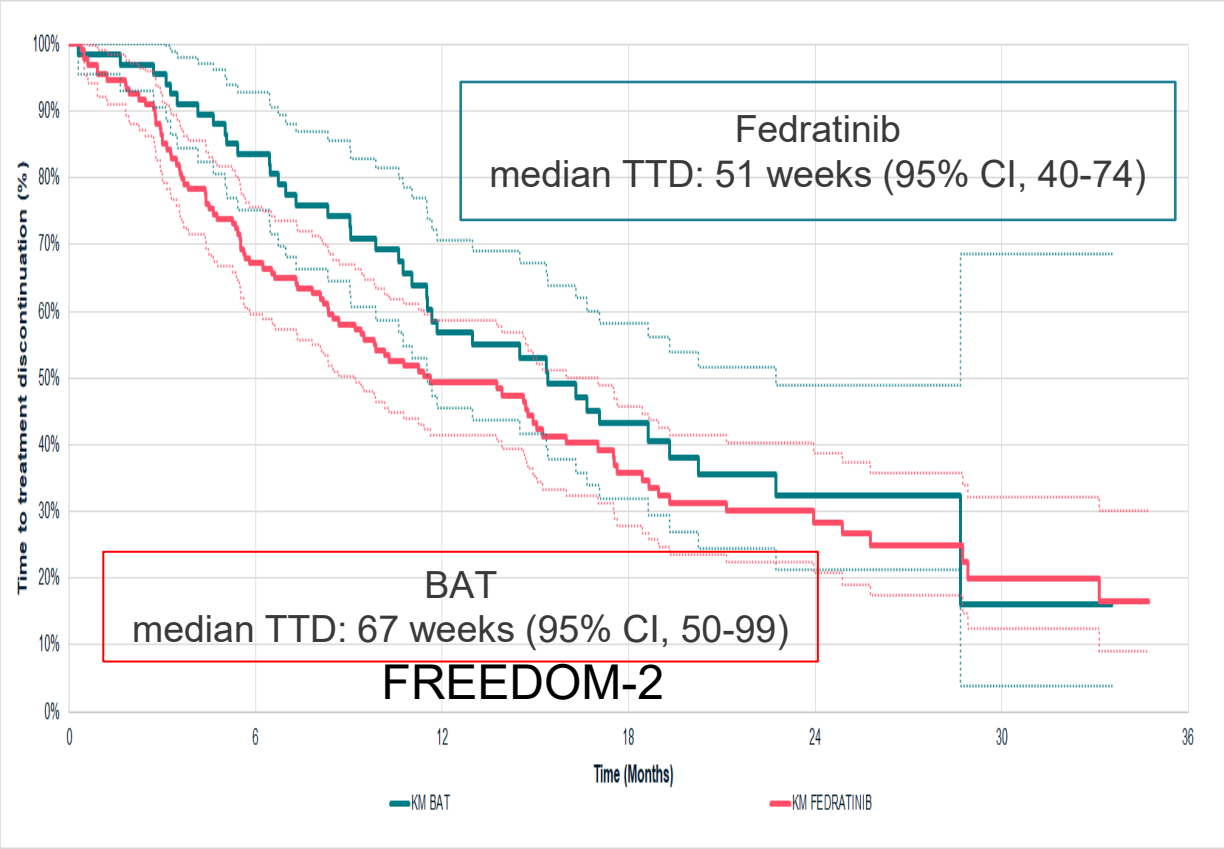
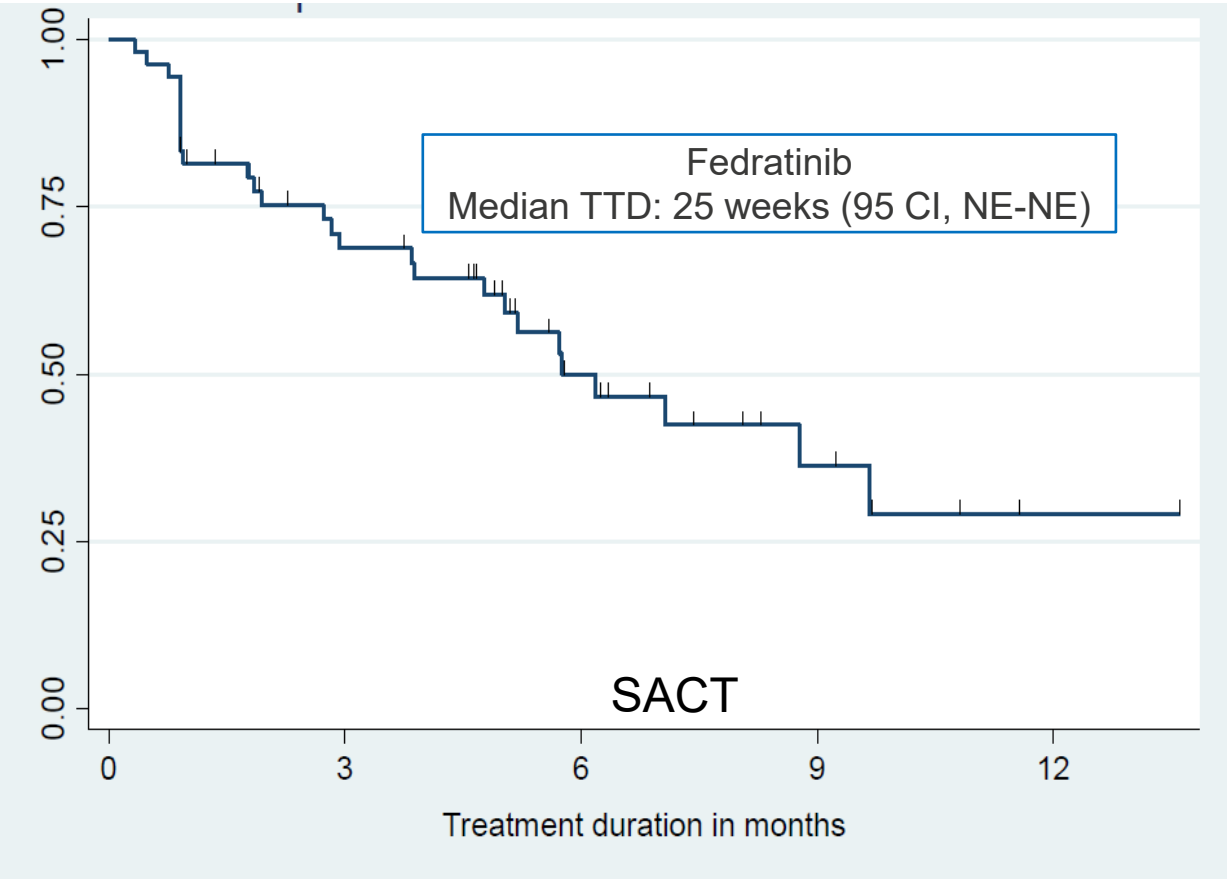
Are baseline characteristics from FREEDOM-2 and SACT similar?

Abbreviations: BAT, best available therapy; Hb, haemoglobin; NR, not reported; SACT, systemic anti-cancer therapy

FREEDOM-2 & SACT: Time to treatment discontinuation (TTD)

EAG: treatment duration shorter in SACT than FREEDOM-2





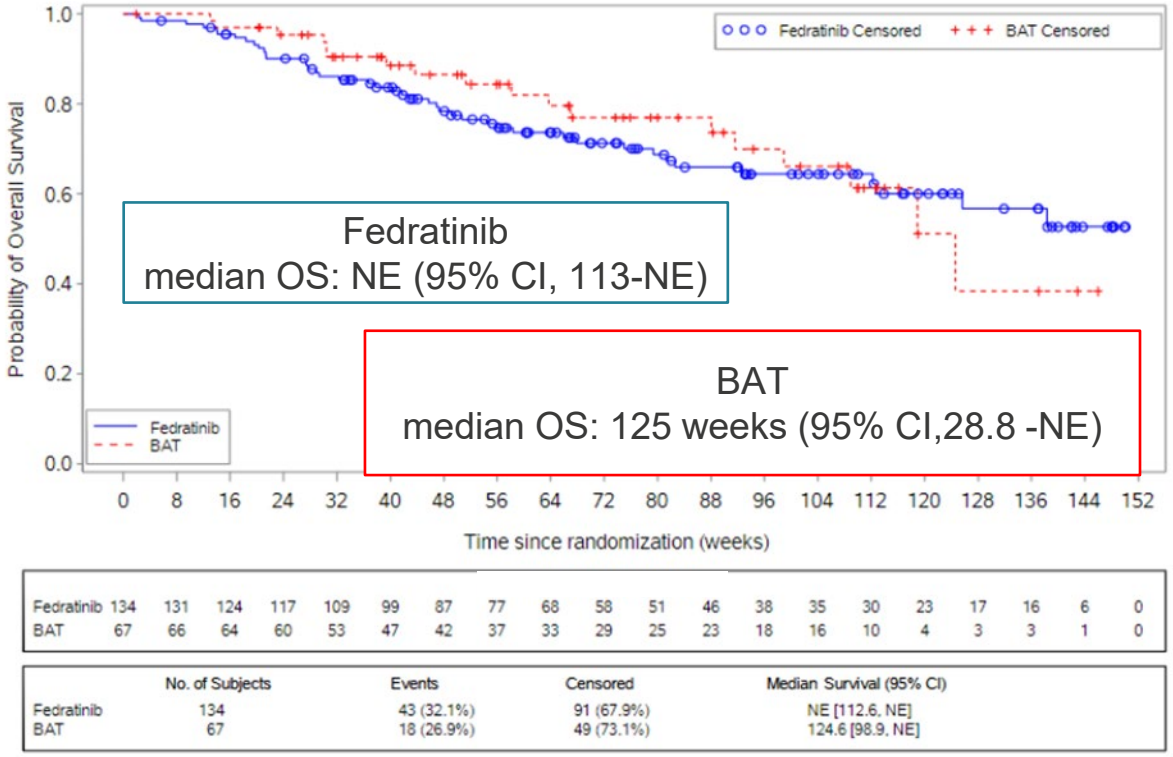
Source: EAG report, Figures 5 and 6

Abbreviations: BAT, best available therapy; CI, confidence intervals; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation

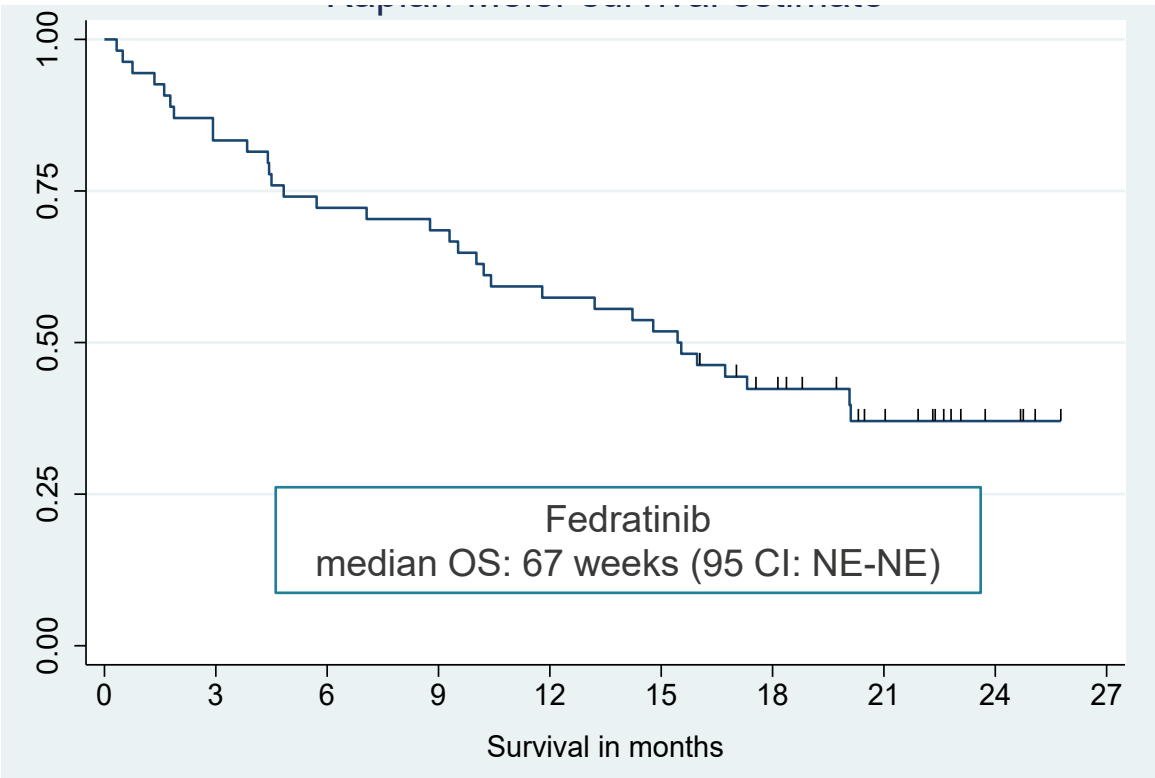
FREEDOM-2 & SACT: Overall survival:

EAG: OS shorter in SACT than FREEDOM-2

FREEDOM-2



SACT



Source: EAG report, Figure 8 and 9

Abbreviations: BAT, best available therapy, CI, confidence intervals; NE, not estimable; OS, overall survival; SACT, systemic anti-cancer therapy;

Key issues: High proportion of people cross over from BAT to fedratinib in FREEDOM-2

Large impact

Background

- Switching from BAT to fedratinib in FREEDOM-2 makes it difficult to compare outcomes beyond 6 months
- Because of switching, company assumed same TTD and OS for BAT in model

Company

- 69% people switched from BAT to fedratinib; with 93% switching after 6 cycles and 7% earlier
- Explored 5 formal methods to adjust for treatment switching but considered none appropriate

EAG

- Agreed none of the formal methods appropriate
- KM estimates from BAT stratified by crossover status show better OS for those who switch
- 21 people did not switch to fedratinib, making OS estimates uncertain
- People with better prognosis are more likely to switch to fedratinib
- Censoring at switching time favours fedratinib by removing people with better prognosis out of BAT

Source: EAG report, Figure 10

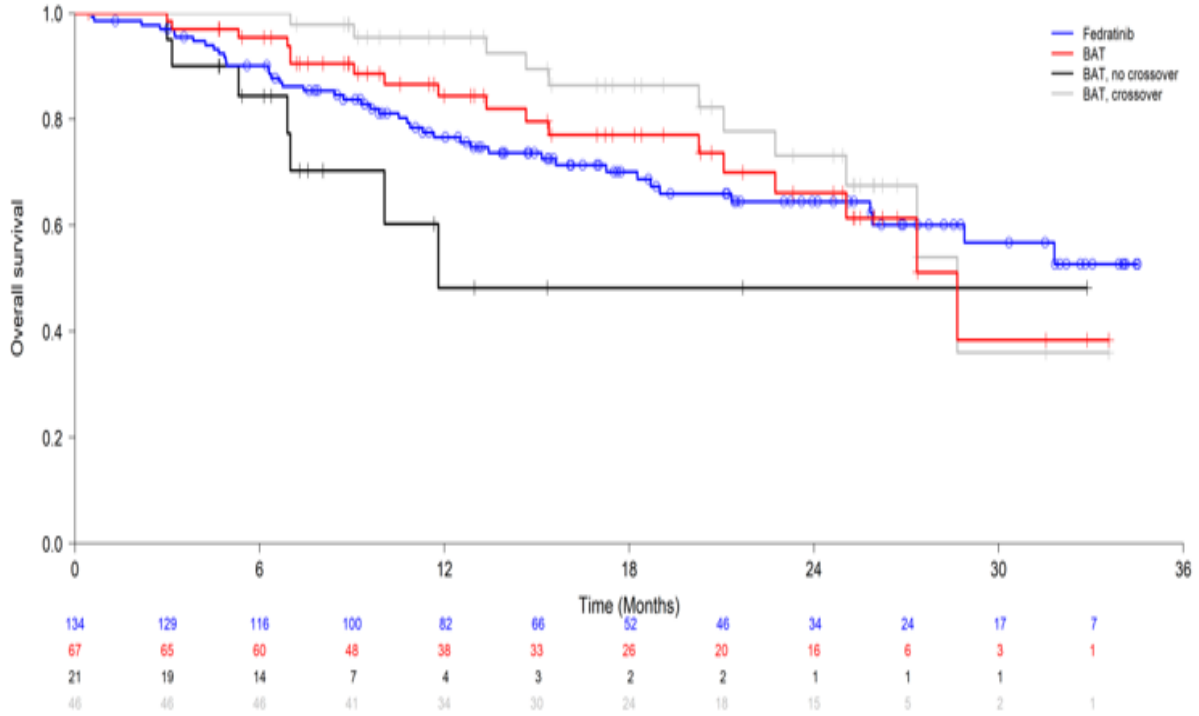


Figure: OS Kaplan-Meier for fedratinib and BAT ITT populations and BAT stratified by crossover status

Abbreviations: BAT, best available therapy, ITT, intention- to-treat; OS, overall survival; SACT, systemic anti-cancer therapy;

Is it appropriate to assume the same TTD and OS for fedratinib and BAT?

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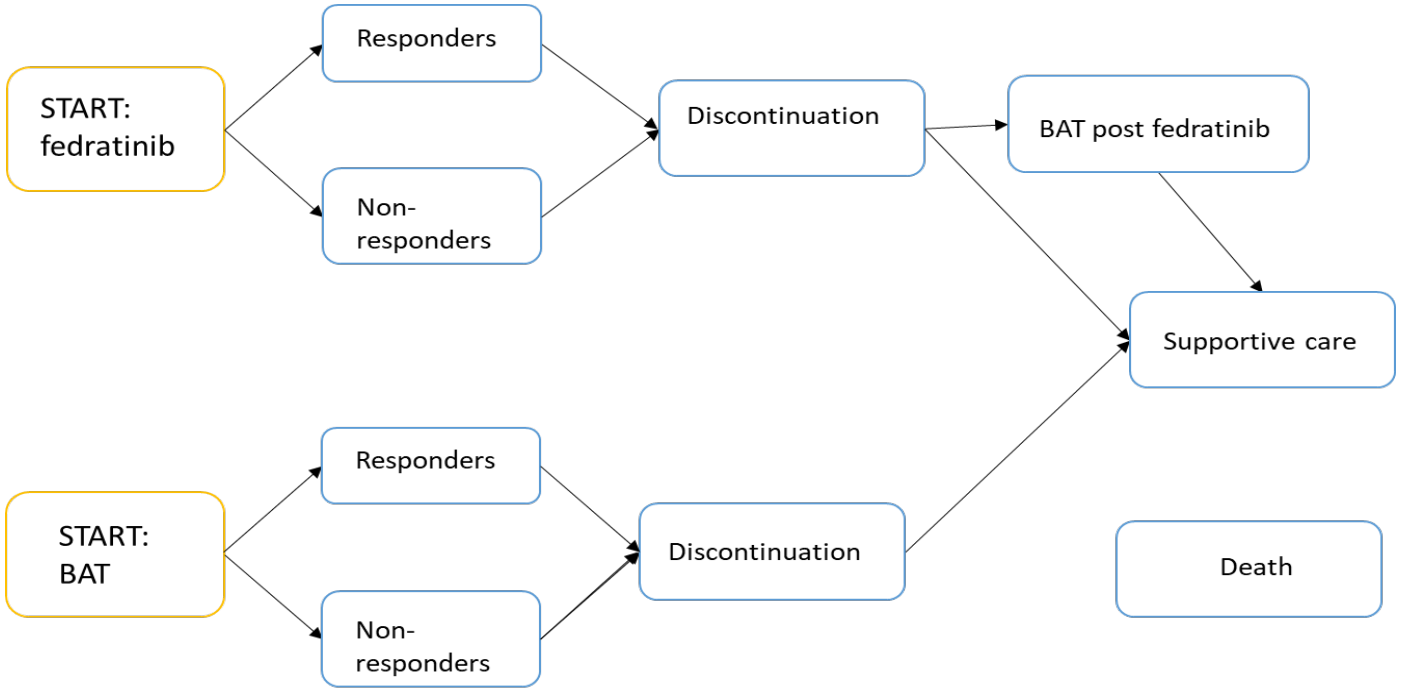
Company's model overview



Source: EAG report, Figure 13

Assumptions with greatest ICER effect:

- Drug wastage for ruxolitinib for dose adjustments
- OS & TTD = between trial arms
- OS & TTD from FREEDOM-2 generalisable to clinical practice

EAG

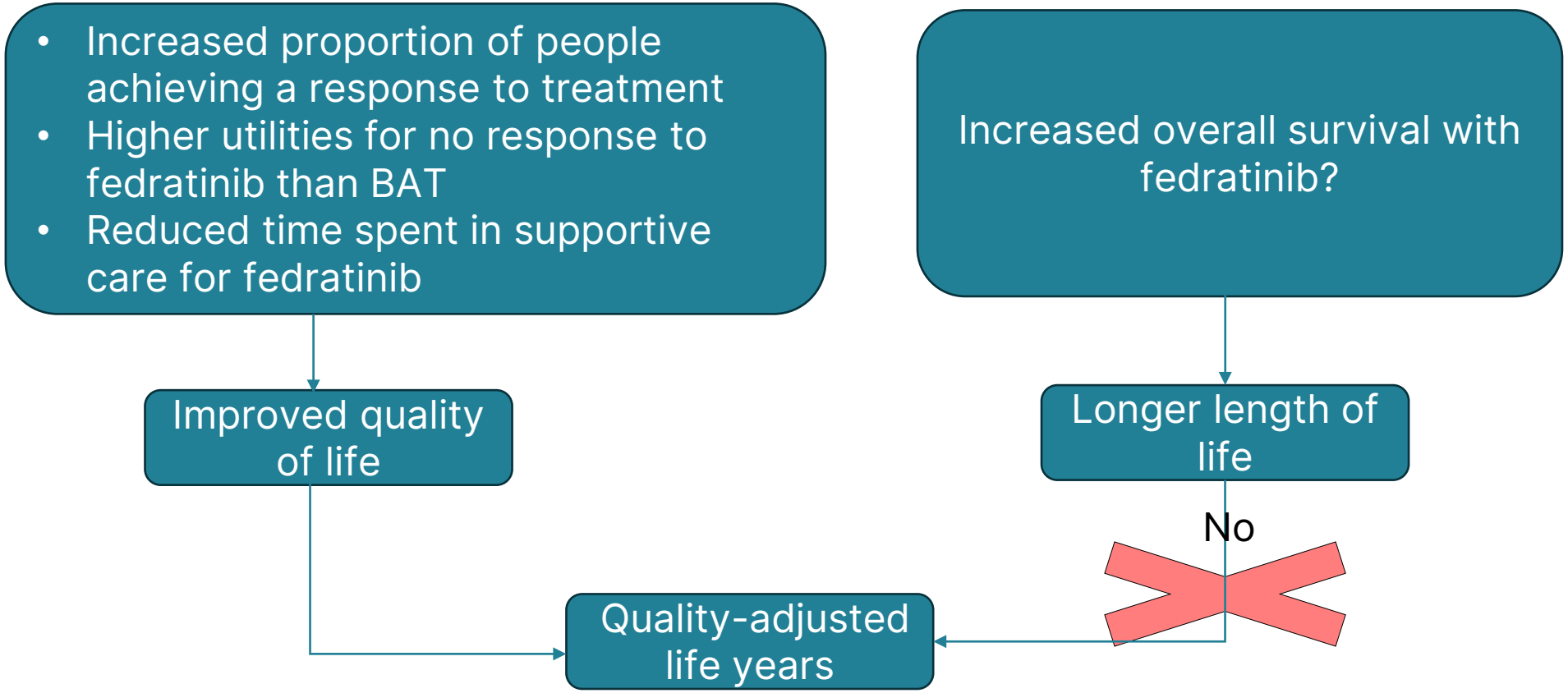
- Model structure differs from TA756 in 3 ways:
  1. DOR not sampled separately i.e.; disease assumed to respond until discontinuation
  2. Excluded AML state
  3. Replacement of 'palliative care' state with 'supportive care' in final 8 week of life after discontinuing fedratinib or BAT
- Identified errors in model:
  1. Utility multiplier for females used for both sexes, double AML rates for BAT
  2. Using sex-specific utility values
  3. PSA producing different life-year outcome
  4. Error related to when discounting starts for supportive care stating
- Used MF-8D utility values instead of EQ-5D from FREEDOM-2

Abbreviations: AML, acute myeloid leukaemia; BAT, best available therapy, DOR, duration of response; MF-8D, myelofibrosis- 8-Dimension; OS, overall survival; PSA; probabilistic sensitivity analysis; TTD, time to treatment discontinuation

Is the company's model structure appropriate?

Supplementary slide

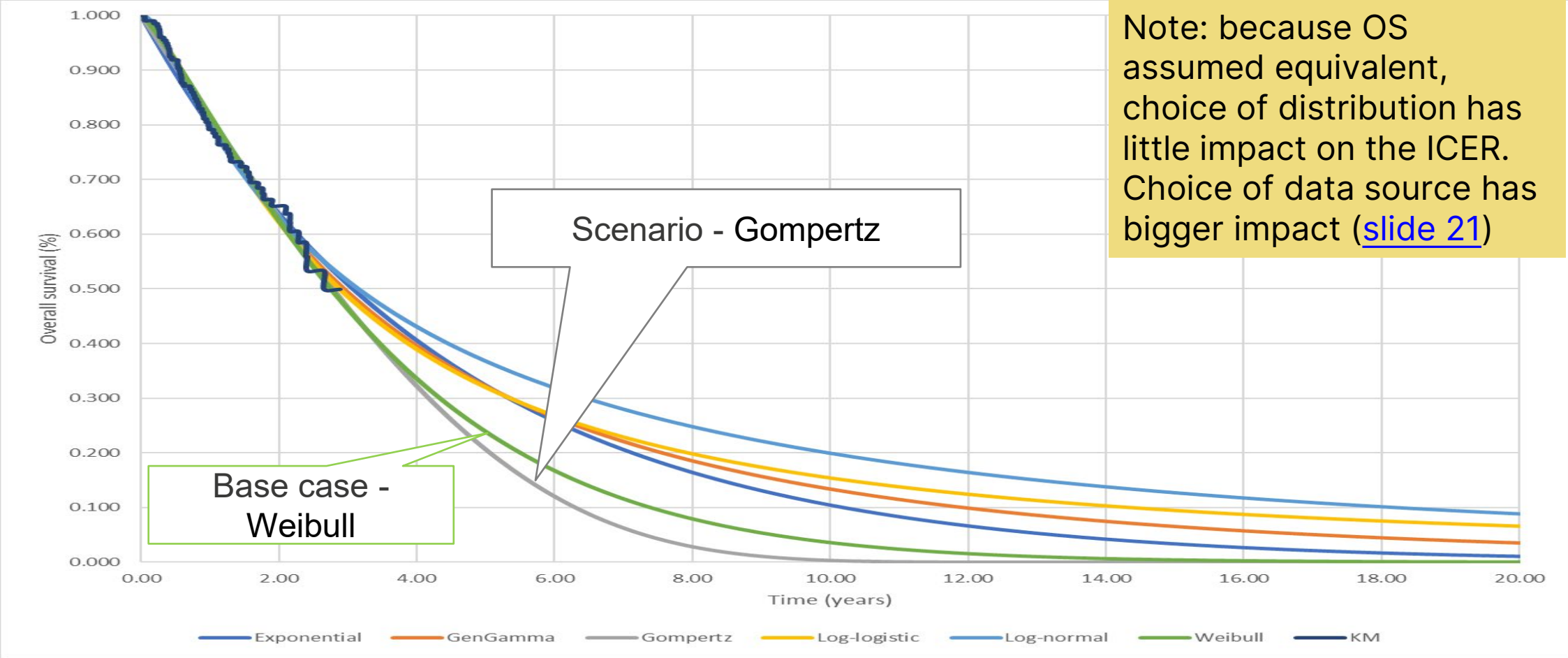
How quality-adjusted life years accrue in model



Abbreviations; BAT, best available therapy

Model output: Overall survival for pooled fedratinib/BAT

- No formal adjustment considered appropriate by both company and EAG
- Company pooled data across fedratinib and BAT arms assuming equivalent OS because observed OS and TTD were similar across fedratinib and BAT arms



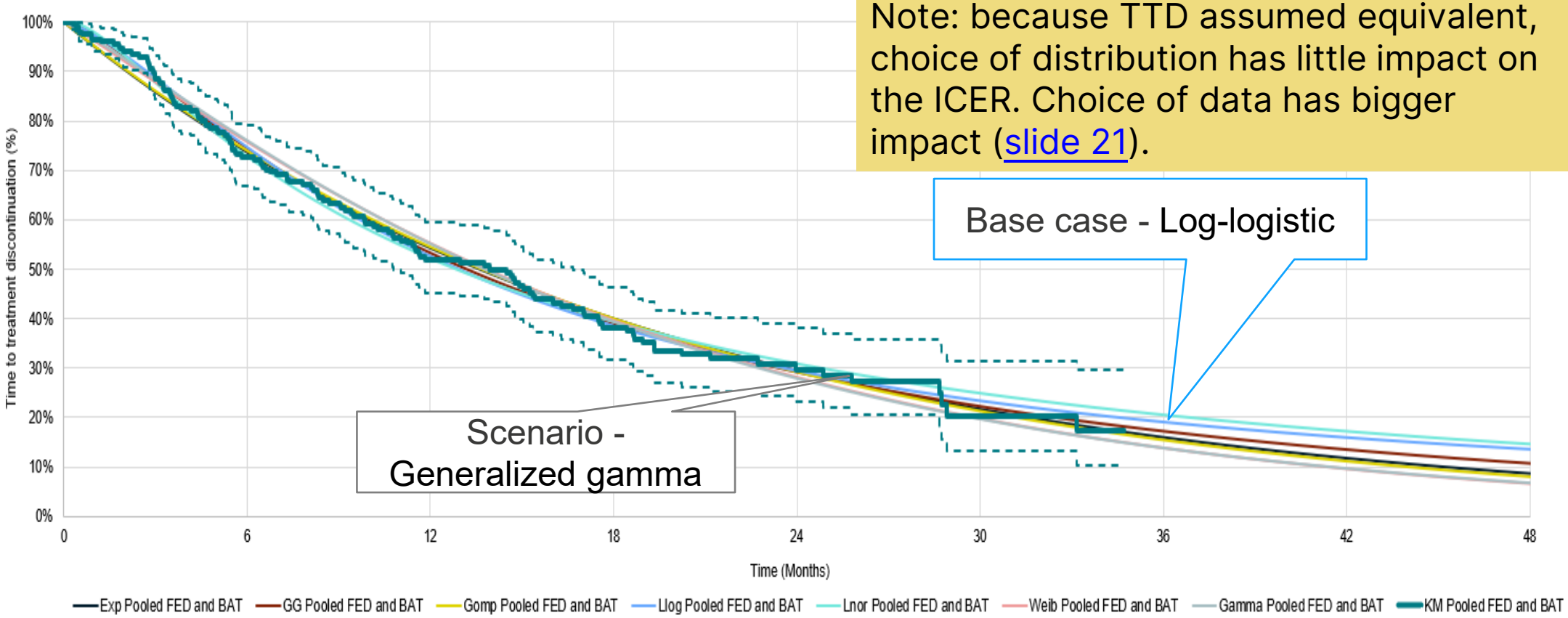
Note: because OS assumed equivalent, choice of distribution has little impact on the ICER. Choice of data source has bigger impact (slide 21)

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

Source: EAG report, Figure 14

Model output: Time to treatment discontinuation (TTD) for pooled fedratinib/BAT

Note: because TTD assumed equivalent, choice of distribution has little impact on the ICER. Choice of data has bigger impact (slide 21).



Source: EAG report, Figure 15

Abbreviations: BAT, best available therapy; FED, fedratinib; KM, Kaplan Meier

Large impact

Key issues: OS and TTD from FREEDOM-2 overestimate TOT & OS expected in clinical practice

Source: EAG report, Figure 19

Background

- Median TTD and OS longer in FREEDOM-2 than SACT

Company

- SACT included older people (median age 72) than FREEDOM-2 (median age 70), had large proportion of males as compared with females (76% vs. 56%) and had 48% missing PS scores
- Real-world data less certain than clinical data, SACT data variable due to diverse characteristics, comorbidities and treatment histories which could affect TTD

Figure: OS and TTD applied in both treatment arms using SACT data

EAG

- SACT population more likely to reflect where fedratinib will be used in clinical practice as fedratinib's proposed use is same as before and people in SACT dataset have received it through the CDF
- Consider model may overestimate both time on treatment and OS in people who receive fedratinib
- Explored a scenario using SACT data to extrapolate TTD and OS in both the fedratinib and BAT arms

Abbreviations: BAT, best available therapy, CDF, Cancer Drugs Fund; OS, overall survival; PS, performance scope; SACT, systemic anti-cancer therapy; ToT, time on treatment; TTD, time to treatment discontinuation

Should the clinical data in the model be based on FREEDOM-2 or SACT?

Key issues: Composition of BAT received after fedratinib

Large impac

Background

- Company model assumed for people with myelofibrosis whose disease did not respond or partially responded with fedratinib will not have any subsequent treatment with fedratinib

Company

- Therapies used in BAT as comparator and subsequent BAT after fedratinib differ as people cannot have ruxolitinib as part of subsequent BAT after fedratinib

Table: Composition of BAT in company base case

Treatment (BAT)	BAT (comparator)	BAT after fedratinib
Ruxolitinib	77.6%	0%
Danazol, hydroxycarbamide, interferon alfa, prednisolone, prednisone, thalidomide	1.5% each	16.7% each
Fedratinib	0%	0%

EAG: TA756: clinicians would not stop fedratinib if disease does not respond due to no treatments available

- Assumed 77.6% will have suboptimal fedratinib = people having suboptimal ruxolitinib in BAT (FREEDOM-2)
- Consider its assumption extends duration of fedratinib as compared to TTD from FREEDOM-2: aligns better with potential use of fedratinib in clinical practice where it may be used until loss of clinical benefit

Abbreviations: BAT, best available therapy; TTD, time to treatment discontinuation

Should BAT after fedratinib include suboptimal fedratinib?

Treatment pathway

Large impact

Key issues: Uncertainty regarding duration of suboptimal ruxolitinib within BAT

Background

- Uncertainty regarding duration of suboptimal ruxolitinib within BAT
- TTD applied in company base case may overestimate ToT with BAT

Company

- Assumed people could cross over on disease progression or within 28 days of end of cycle 6
- Fitted parametric curves to TTD to KM curve which include ToT with fedratinib for people who switched from BAT to fedratinib

EAG

- TTD curves for BAT included time spent on fedratinib because people crossing over from BAT to fedratinib were not censored at crossover in KM plot for TTD
- Most people in FREEDOM-2 crossed over after 6 months: consider cross over not driven by disease progression but by individual's choice to have fedratinib instead of BAT
- Uncertain if the duration on BAT would have been similar without the option to cross over to fedratinib
- Fedratinib might have replaced suboptimal ruxolitinib in FREEDOM-2, so the total expected JAK use duration would be similar; uncertain if an equivalent OS would be expected with a shorter duration of BAT
- Explored scenario analysis where TTD and OS curves fitted to BAT excluded people who crossed over to fedratinib

Abbreviations: BAT, best available therapy; JAK, Janus associated kinase KM, Kaplan-Meier; OS, overall survival; ToT, time on treatment; TTD, time to treatment discontinuation

Is the company approach to model suboptimal ruxolitinib within BAT appropriate?

Key issues: Transition to supportive care after fedratinib

Large impact

Background
- Model assumed some people transition to supportive care after fedratinib rather than to BAT

Company
- Assumed proportion transitioning to supportive care after fedratinib higher for disease with no response (66.7%) and lower (33.3%) for disease which responds initially and then stops responding
- Proportion transitioning to supportive care after BAT=100%, including those having ruxolitinib as part of BAT

EAG
- Transition to supportive care - associated with lower utility in model - was delayed for people having fedratinib vs. BAT, providing an indirect QALY benefit for fedratinib, including non-responders
- People whose disease does not respond to fedratinib can have further treatment with non-JAK forms of BAT while for people whose disease does not respond to ruxolitinib have supportive care
- Explored a scenario with 100% of people stopping fedratinib go directly onto supportive care with no BAT as subsequent treatment
- Alternative method would include a proportion of people who had ruxolitinib as comparator BAT to transition to other forms of BAT after discontinuing ruxolitinib: cannot be implemented in current model structure

Is the company's assumption of transitioning straight to supportive care after BAT appropriate?

Abbreviations: BAT, best available therapy; JAK, Januse Kinase; QALY, quality-adjusted life years

Key issues: Utility gains in disease with no response to fedratinib and BAT

Large impact

Background

- Company's model assumed no change in utility from baseline for people with no response to BAT but applied an increase in utility of 0.052 from baseline for people with no response to fedratinib

Company

- Used a regression model to calculate health utilities for fedratinib and BAT, adding results to baseline utilities

EAG

- Applying utility gain for no response for only fedratinib problematic
- Noted regression analysis did not include treatment allocation as a covariate
- Applied non-responder utility gain from regression analysis to everyone not achieving treatment success, regardless of their treatment

Table: Utilities applied in model

Status		Utility value	Utility gain
Baseline		0.649	NA
No response	Fedratinib	0.701	Yes
	BAT	0.649	No
Response	Fedratinib	0.817	NA
	BAT		

0.052 utility gain for JAK non-response

Is it appropriate to assume utility gain for no response to fedratinib only?

Abbreviations: BAT, best available therapy; JAK, Januse Kinase; NA, not applicable

Large impact

Key issues: Costing of ruxolitinib assumes high wastage due to dose changes

Background

- Mean dose of ruxolitinib in BAT arm of FREEDOM-2 was 24.1 mg but model included [redacted]mg (equivalent)

Company

- Model assumed every time a new dose recorded mid-cycle, remaining pack was discarded and a new pack of 4 weeks was prescribed
- In clinical practice when a new dose is prescribed, tablets from the old dose are unlikely to be used

EAG

- Acknowledge some ruxolitinib wastage from AEs but the company's model overestimate: average daily dose of [redacted] mg/ person much higher than 24.1mg
- [redacted] to [redacted] packs being prescribed per person/ cycle across first 6 cycles, when a single pack would usually provide 1 cycle of treatment: unlikely this wastage occurs in clinical practice
- Dose of ruxolitinib depends on platelet count with haematology tests required on day 1 and 15 of cycles 1 to 3 while model assumed every 3 weeks
- NHS would not routinely prescribe for a 4-week period if dosing was dependent on a test every 2 weeks
- Preferred to use a dose of 23.8 mg with 5% wastage for dose adjustment for first 6 weeks cycle

How much wastage is expected in clinical practice?
How frequently are people reviewed in NHS practice?

Abbreviations: AEs, adverse events; BAT, best available therapy

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Other considerations

Equality considerations and severity: no issues identified

- Company submission does not make a case for severity weighting
- EAG advises no severity modifier should be applied given the calculated QALY shortfall (weight of 1.0 should be applied)
- Company states that no equality issues were identified relevant to access of fedratinib
- One stakeholder highlighted unmet need for additional treatment options in older patients who are ineligible for stem cell transplantation and are at disadvantaged compared to younger people

Other issues: RBC transfusion & sex-specific utilities modelling

RBC transfusion modelling

- EAG: inconsistent approach - RBC transfusions were allowed on BAT and fedratinib; for people having fedratinib RBC transfusions not accounted in model
- EAG preferred to assume RBC transfusion rate was equal between fedratinib and BAT, provide scenario but had little impact on ICER

Sex-specific utilities modelling

- EAG: in regression model, considerable difference in baseline utility by sex (0.579, females, 0.711, males)
- Company's model had the option to use different utility values by sex, but the company only adjusted for age-related decrements
- Consider using gender-specific utilities a reasonable alternative approach because it captures treatment effect of fedratinib and difference in baseline utility

Abbreviations: BAT, best available therapy; RBC, red blood cells

Other issues: Definition of response using spleen volume/symptoms

Company

- Model defines response as those people with spleen volume response ≥ 35% or symptom response ≥ 50% with an equal gain in health-related quality of life

EAG

- Disagree with the company's combined definition because clinical opinion suggests these measures track each other but FREEDOM-2 shows low agreement between them
- Company's regression using individual definition suggests higher utility gain associated with symptom response than spleen volume
- Presented 2 scenario analyses using individual response rates for spleen volume and symptom response but had little impact on ICER

Table: Regression output from FREEDOM-2

Outcome	Utility estimate
Speen or symptom response	0.115
Spleen response	0.072
Symptom response	0.135

Abbreviations: ICER, incremental cost-effectiveness ratio

Supplementary appendix

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Suboptimal treatment	No suboptimal fedratinib usage as part of BAT after fedratinib	Suboptimal fedratinib % = suboptimal ruxolitinib % in BAT
Utilities	• 0.052 utility gain for fedratinib non-responders • No utility gain for BAT non-responders	0.052 utility gain for all non-responders (both fedratinib and BAT)
Ruxolitinib wastage	• Higher wastage (every time a new dose recorded mid-cycle, remaining pack was discarded and a new pack of 4 weeks was prescribed)	• Average initial dose across first 6 cycles in FREEDOM-2 • 5% wastage
BAT composition	Excluded hydroxyurea from BAT	All treatments used in BAT
RBC transfusion rate	Lower transfusion rate for fedratinib	Fedratinib = BAT
Model inputs & errors	Old eMIT prices with errors not corrected	Updated eMIT prices and corrected errors (post clarification)

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Abbreviations: BAT, best available therapy, eMIT, Electronic market information tool; RBC, red blood cells

Key issues and questions for committee

Issues for committee discussion		Slide
Decision problem	• Is momelotinib a relevant comparator for fedratinib?	See slide
Clinical evidence	• Given the high rate of crossover at 6 months, is it appropriate to assume TTD and OS are the same for fedratinib and BAT?	See slide
Cost-effectiveness	• Should BAT after fedratinib include suboptimal fedratinib?	See slide
	• Is the company's assumption of transitioning to supportive care appropriate?	See slide
	• Is it appropriate to assume utility gain for no response to fedratinib only?	See slide
	• How much wastage is expected in clinical practice? • How frequently are people reviewed in NHS practice?	See slide
	• Is the company approach to model suboptimal ruxolitinib within BAT appropriate?	See slide
	• Should FREEDOM-2 or SACT be used to model clinical outcomes?	See slide

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Abbreviations: BAT, best available therapy, OS, overall survival: TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discount

Analyses to be presented include:

- Company and EAG base cases
  - Company base suggests fedratinib slightly more effective and less expensive than BAT (dominant)
  - EAG base case suggests fedratinib slightly more effective but more expensive than BAT (ICER above £100,000/QALY)
- EAG scenario analyses
  - Using OS and TTD data from SACT further increases the ICER

Abbreviations: BAT, best available therapy; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation

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Thank you.

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Supplementary appendix

FREEDOM-2: Spleen & symptom response at 6 months

Higher spleen volume response and symptom response rate for fedratinib compared with BAT

Table: FREEDOM-2: Spleen volume response and symptom response at EOC6

Outcome	Measure	Fedratinib (N=134)	BAT (N=67)	Difference, *p*-value[b]
Spleen volume response rate ≥ 35%	≥ 35% SVR at EOC6[a]	48 (36%)	4 (6%)	30%, p<0.0001
Spleen volume response rate≥ 25%	≥ 25% SVR at EOC6[a]	63 (47%)	9 (13%)	34%, p<0.0001
Symptom response rate	≥ 50% TSS reduction at EOC6[a]	43 (34%) (analysed N=126)	11 (17%) (analysed N=65)	17%, p=0.0033
Spleen volume or symptom response	≥ 35% SVR or ≥ 50% TSS reduction at EOC6[a]	70 (52%)	13 (19%)	33%, *p*=NR

[a] People with missing assessment at EOC6, including those who met the criteria for progression of splenomegaly before EOC6, were considered non-responders

[b] Between-group difference according to stratified analysis based on electronic case report form

Used in model

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Abbreviations: BAT, best available therapy; EOC6, end of cycle 6; SVR, spleen volume reduction; TSS, total symptom score.

Main slide

FREEDOM-2: Anaemia response and RBC transfusion dependency

Table: FREEDOM-2: Anaemia response and red blood cell transfusion dependency

Outcome		Fedratinib (N=134)	BAT (N=67)
Anaemia response at any time		20/101 (20%)	12/53 (23%)
RBC transfusion rate (unit per patient per 28 days): mean (SD), N analysed		1.935 (2.0898), N=96	1.408 (1.2085), N=42
Baseline RBC transfusion dependence	**Dependent**	29/134 (22%)	11/67 (16%)
	Independent	105/134 (78%)	56/67 (84%)
Postbaseline RBC transfusion independence	**Dependent**	28/29 (97%)	9/11 (82%)
	Independent	1/29 (3%)	2/11 (18%)
Postbaseline RBC transfusion dependence	**Dependent**	25/105 (24%)	19/56 (34%)
	Independent	80/105 (76%)	37/56 (66%)
Platelets transfusion rate (unit per person per 28 days):mean (SD), N analysed		0.487 (0.7253), N=20	2.843 (5.7614), N=7

Source: EAG report, table 14

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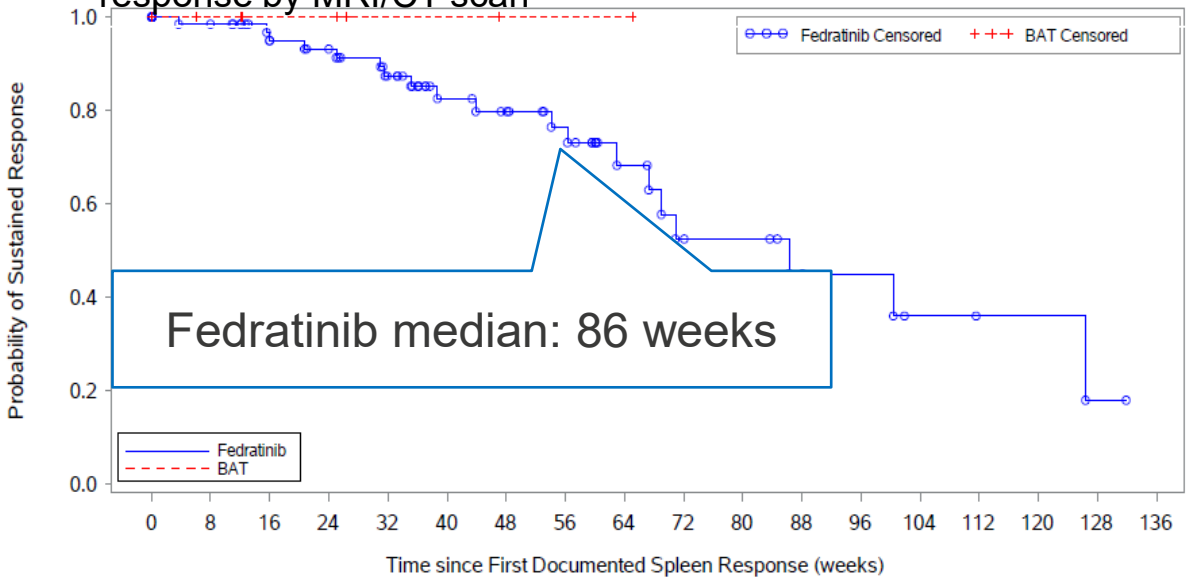
Abbreviations: BAT, best available therapy; RBC, red blood cell; SD, standard deviation

FREEDOM-2: Durability of spleen volume response & symptom response

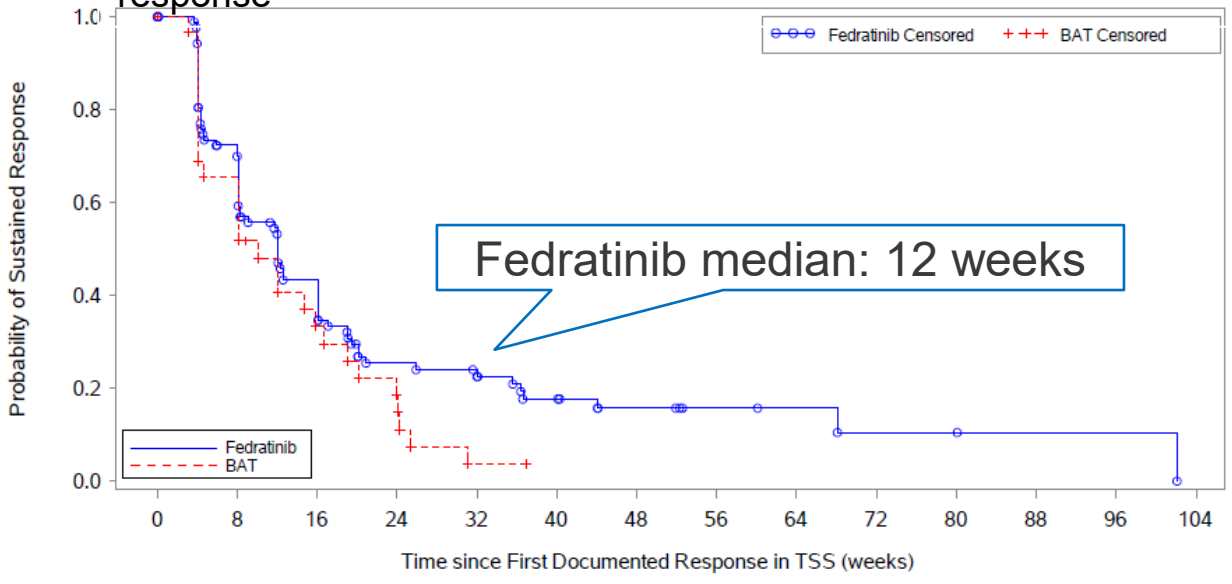
Figure: FREEDOM-2: Kaplan-Meier plot of durability of spleen volume response by MRI/CT scan



No. of Subjects at Risk																	
Fedratinib	72	64	55	51	43	31	28	23	14	10	9	6	5	3	2	2	1	0
BAT	8	6	4	4	2	2	1	1	1	0	0	0	0	0	0	0	0	0

	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	72	19 (26.4%)	53 (73.6%)	86.3 [63.0, 126.4]
BAT	8	0 (0.0%)	8 (100.0%)	NE [NE, NE]

Figure: FREEDOM-2: Kaplan-Meier plot of durability of symptom response



No. of Subjects at Risk																	
Fedratinib	90	61	35	18	16	11	7	4	3	2	2	1	1	0			
BAT	32	19	9	6	1	0	0	0	0	0	0	0	0	0			

	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	90	70 (77.8%)	20 (22.2%)	12.1 [8.1, 16.1]
BAT	32	27 (84.4%)	5 (15.6%)	10.1 [4.1, 16.7]

Source: EAG report, Figure 3 and 4

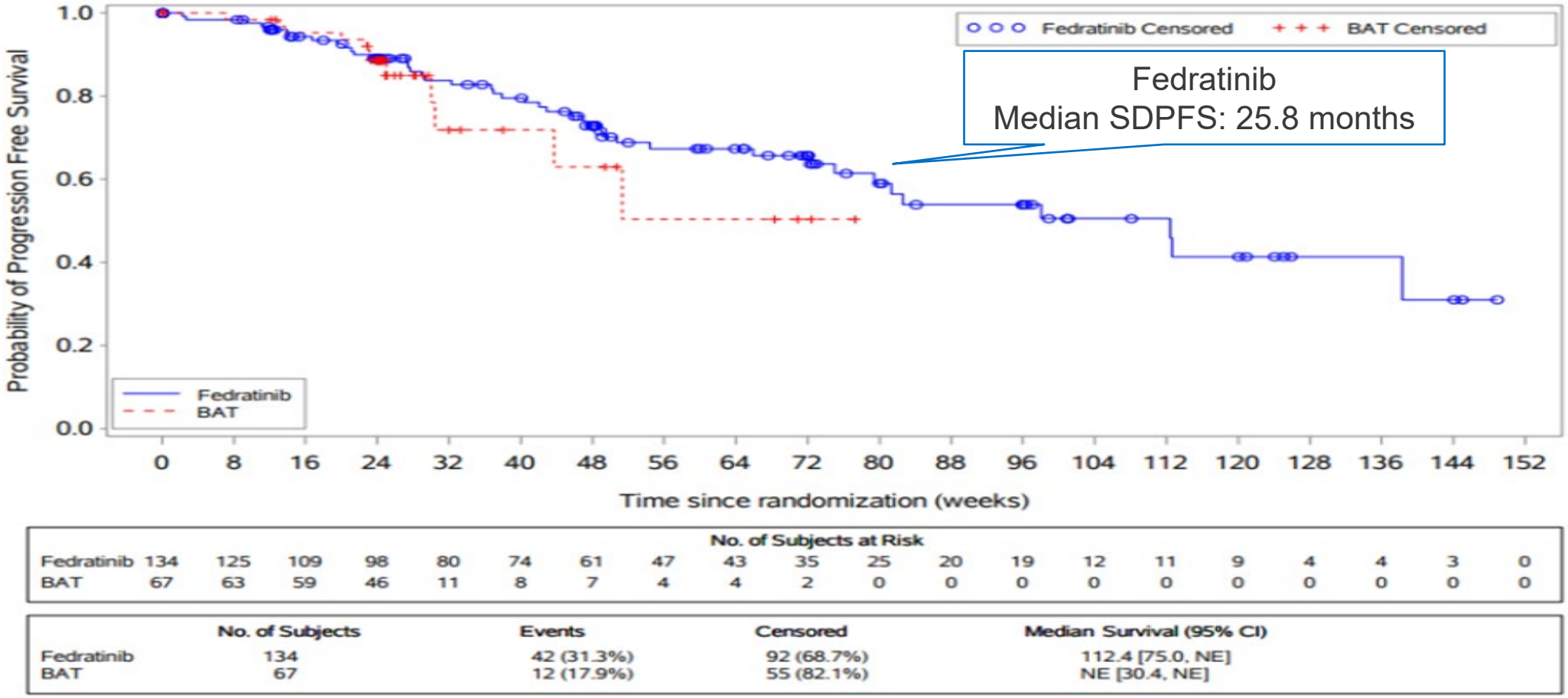
Abbreviations: CI, confidence intervals; CT, computed tomography; MRI, magnetic resonance imaging; NE, not estimable

FREEDOM-2:Spleen and disease progression-free survival (SDPFS)

Company: no censoring for cross over

EAG: Censoring at point of initiation of anti-myelofibrosis therapy

Figure: FREEDOM-2: SDPFS



No. of Subjects at Risk

Fedratinib	134	125	109	98	80	74	61	47	43	35	25	20	19	12	11	9	4	4	3	0
BAT	67	63	59	46	11	8	7	4	4	2	0	0	0	0	0	0	0	0	0	0

	No. of Subjects	Events	Censored	Median Survival (95% CI)
Fedratinib	134	42 (31.3%)	92 (68.7%)	112.4 [75.0, NE]
BAT	67	12 (17.9%)	55 (82.1%)	NE [30.4, NE]

Source: EAG report, Figure 7

Abbreviations: BAT, best available therapy, CI, confidence intervals; NE, not estimable;

Other issues: Companies' deviation from NICE reference case

Element of HTA	Reference case	Adherence yes/no
Population	The scope developed by NICE	No: population narrower (post ruxolitinib)
Intervention	As per NICE scope	Yes: but as/licence but ToT contrast SPC*
Comparator	As per NICE scope	No: excluded momelotinib
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	No: fully incremental vs. momelotinib required for relevant subgroup
Synthesis of evidence on health effects	Based on systematic review	No: not provided updated SLR: outcomes from FREEDOM-2 & literature
Measuring and valuing health effects	Health effects should be expressed in QALYs. EQ-5D is preferred measure of HRQoL in adults	No: MF-8D from FREEDOM-2
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	No EQ-5D data used or scenarios provided
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No: MF-8D instead of the EQ-5D
Other elements (intervention, perspective on outcomes & costs, time horizon, equity considerations, evidence on resource use and costs and discount rate) are broadly in line with the NICE reference case		

* ToT based on FREEDOM-2 (until disease progression in model contrast SPC which states treatment can continue lack of therapeutic effect

Abbreviations: BAT, best available therapy; EQ-5D, euroQol 5-dimensions, HRQoL, health-related quality of life; MF-8D, Myelofibrosis- 8-Dimension; QALY, quality-adjusted life year; SPC, summaries of product characteristics; ToT, time on treatment

FREEDOM-2: EORTC QLQ-C30 & EQ-5D-5L utility index

Company: Similar increases from baseline in fedratinib and BAT

EAG: People analysed in BAT drop suddenly at EOC6, unclear this includes people who cross over

Figure: EORTC QLQ-C30: mean change from baseline

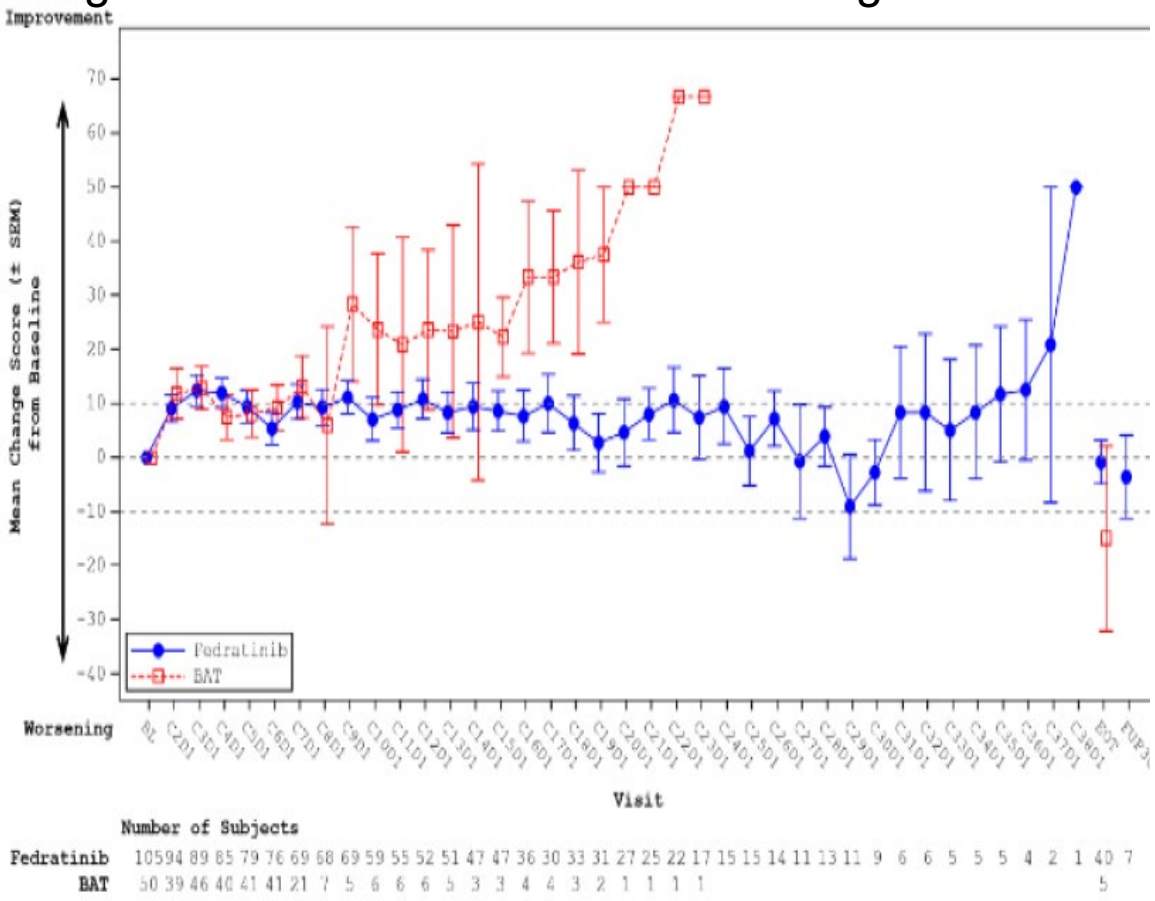
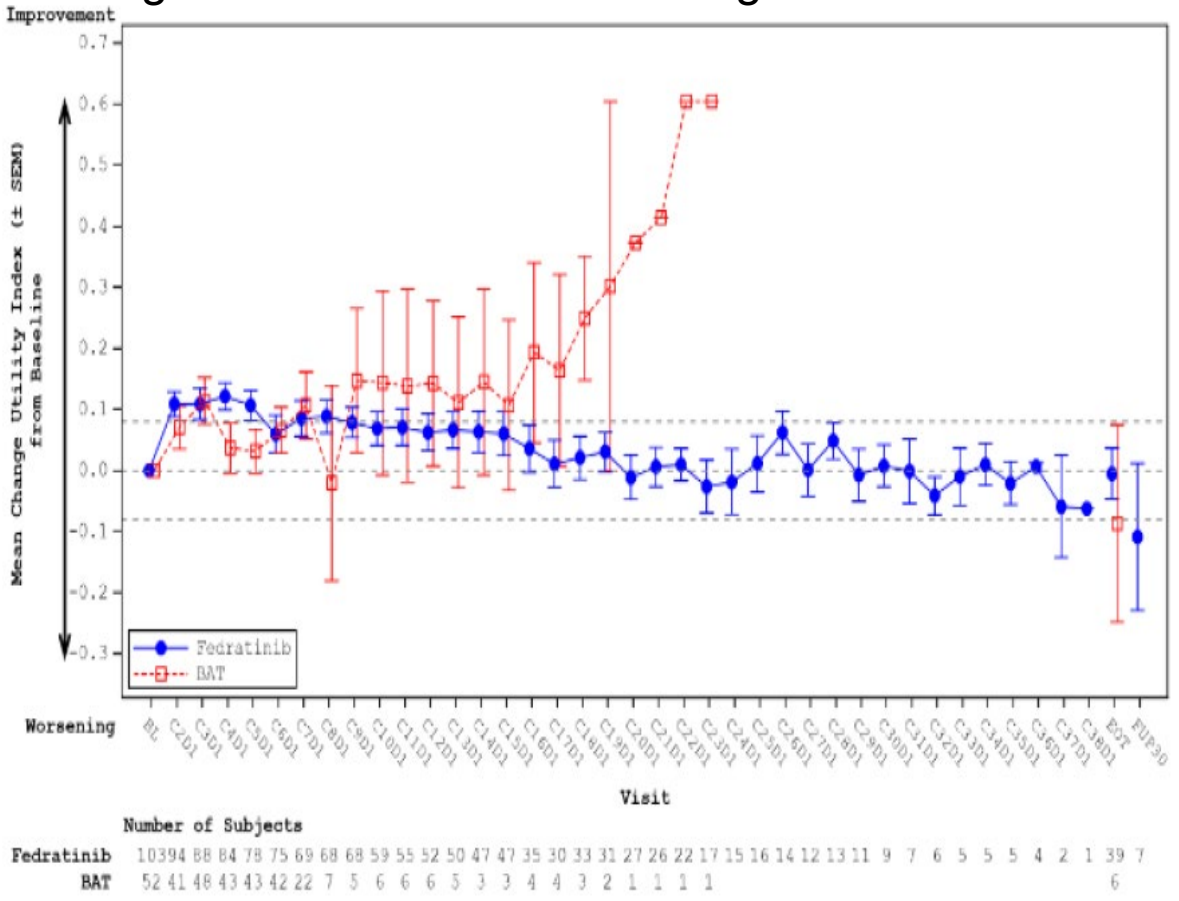


Figure: EQ-5d-5L: mean change from baseline



Source: EAG report, Figure 11 and 12

Abbreviations: BAT, best available therapy; EOC6, end of cycle 6; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients; EQ-5D-3L; EuroQol 5-dimensions - 3-level

Disease-specific utility values applied in model and values obtained from FREEDOM-2

Table :Comparison of disease-specific utility values applied in model and values obtained from FREEDOM-2

Category	Used in model	Category in analysis of FREEDOM-2: MF-8D utilities	Post-baseline MF-8D from FREEDOM-2, Mean (SD)	Predicted by regression
Utilities pooled across males and females (0.649 at baseline) – company's base-case				
No response (FED)	0.701	No response	0.716 (0.203)	0.701
No response (BAT)	0.649			
Response (FED)	0.817	Response	0.824 (0.149)	0.817
Response (BAT)				
Sex-specific utilities – males (0.711 at baseline)				
No response (FED)	0.790	No response	0.750 (0.218)	0.740
No response (BAT)	0.711			
Response (FED)	0.905	Response	0.858 (0.135)	0.855
Response (BAT)	0.855			
Sex-specific utilities – females (0.579 at baseline)				
No response (FED)	0.658	No response	0.680 (0.180)	0.658
No response (BAT)	0.579			
Response (FED)	0.773	Response	0.785 (0.154)	0.773
Response (BAT)				

Abbreviations: BAT, best available therapy, FED, fedratinib, MF-8D, myelofibrosis- 8-Dimension; SD, standard deviation

Decision problem

	Final scope	EAG comments
Population	Adults with disease-related splenomegaly or symptoms of: •Primary myelofibrosis (also known as chronic idiopathic myelofibrosis) • Post-polycythaemia vera myelofibrosis, or, • Post-essential thrombocythaemia myelofibrosis	• Population addressed narrower but consistent with population received fedratinib (in people who had previous ruxolitinib)
Intervention	Fedratinib 400 mg	• As per scope
Comparators	For people whose disease was not previously treated with a JAK inhibitor: • ruxolitinib • momelotinib (subject to NICE evaluation) For people whose disease was previously treated with ruxolitinib or if ruxolitinib is not appropriate • established clinical practice • momelotinib (subject to NICE evaluation)	• No comparison provided momelotinib • Momelotinib is likely to replace suboptimal ruxolitinib in people eligible for treatment with momelotinib
Outcomes	• Spleen size, symptom relief (including itch, pain and fatigue), OS, leukaemia-free survival, response rate, hematologic parameters (including RBC transfusion and blood count), AEs of treatment, HRQoL	Appropriate but highlighted that: • Several definitions of response used in FREEDOM-2 • Combined endpoint of spleen or symptom response was used in the company's economic model

Abbreviations: AEs, adverse events; HRQoL, health-related quality of life; OS, overall survival; RBC, red blood cells

Decision problem

	Final scope	EAG comments
Subgroups	• People whose disease was previously treated with a JAK inhibitor • Prognostic factors such as haemoglobin <10 g/dL, leukocyte count >25 x 109/L, circulating blasts (immature blood cells) ≥ 1%, presence of constitutional symptoms or platelet count	• Company restricted to those patients with previous JAK inhibitor treatment • Subgroup results for the primary outcome from FREEDOM-2 are presented by baseline haemoglobin (≤100g/L and > 100g/L), white blood cell count at baseline (≥25 x 10^9/L and <25 x 10^9/L), blood blasts at baseline (≥1% and <1%), platelet count (50 to 100 and ≥100 x 10^9/L) presence of constitutional symptoms

Abbreviations: JAK, Janus associated kinase

How company incorporated evidence into model

Table: Summary of evidence used to inform the company's model

		Assumptions and evidence source
Model Structure		• Individual patient discrete event simulation
Baseline characteristics		• FREEDOM-2 (age, BSA, weight, proportion of females)
Time horizon		• Lifetime (30 years)
Efficacy		• FREEDOM-2 (both fedratinib and BAT arms for OS, TTD and response rates)
Utilities		• MF-8D data collected in FREEDOM-2
Costs	**Drug acquisition**	• MIMS, eMIT, and BNF
	Disease management	• NHS Reference Costs, Unit Costs of Health and Social Care • Private patient tariff and literature
	AEs	• NHS Reference Costs, Unit Costs of Health and Social Care • TA386 and Literature
	End of life care	• Round et al 2015
Perspective		• NHS and PSS

Abbreviations; AE - adverse event; BNF, British National Formulary; BAT; best available therapy; BSA, body surface area; eMIT; electronic Market Information Tool; MIMS, Monthly Index of Medical Specialities; OS - overall survival; TTD - time to treatment discontinuation

Source: EAG report, table 21

Main slide