Avapritinib for treating advanced systemic mastocytosis [ID3770]

For public – redacted

Technology appraisal committee C [06 August 2024]

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Company: Blueprint Medicines

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Avapritinib for treating advanced systemic mastocytosis [ID3770]

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

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Background on advanced systemic mastocytosis

A rare haematologic neoplasm with severe and debilitating symptoms

Causes

- Characterised by hyperactivation and accumulation of mast cells
- Mutation of *KIT* (encoding a receptor tyrosine kinase) drives ~95% of cases

Epidemiology

- Prevalence in England estimated to be considerably lower than 1:50,000

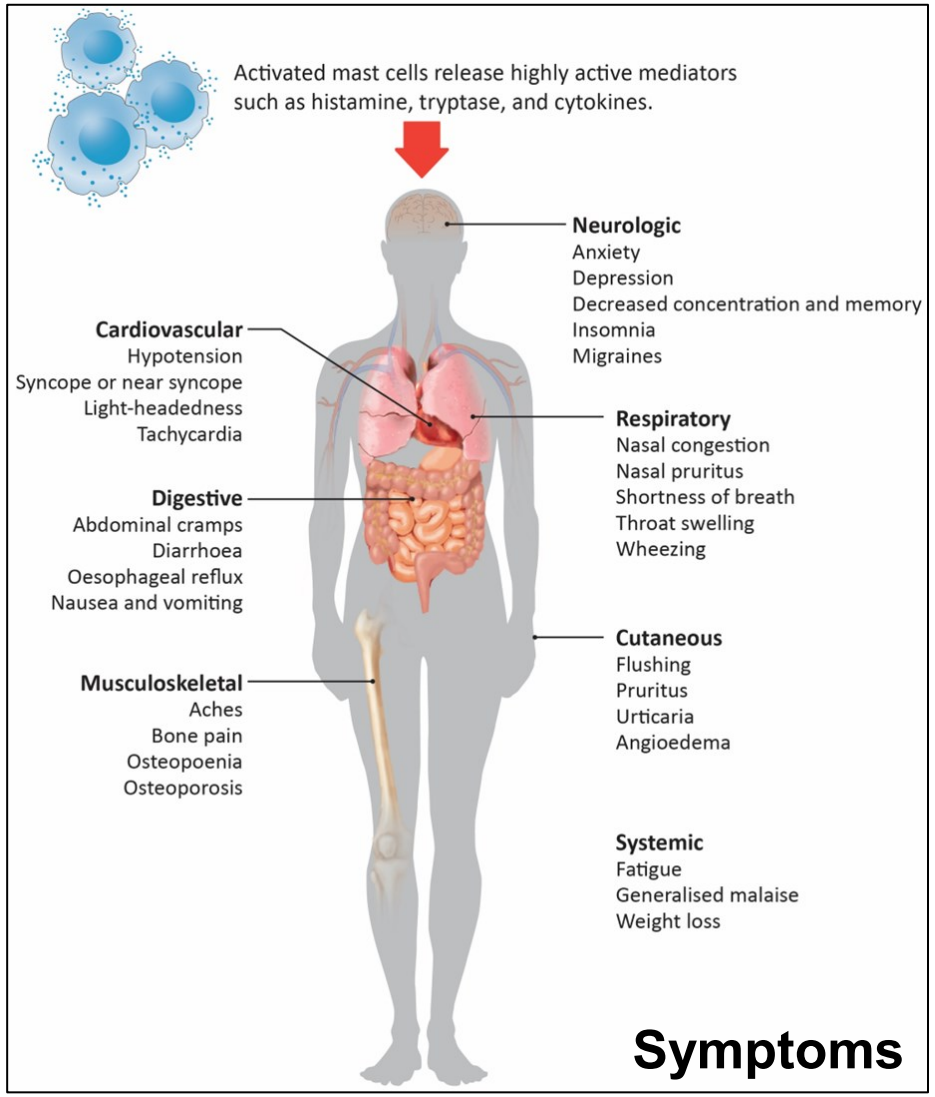
Diagnosis and classification

- 3 disease subtypes; ASM, SM-AHN, MCL

Prognosis and survival

- Reflects subtype; survival ranges from 2 months to 6 years

Figure 2, CS



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ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with associated haematologic neoplasm

Patient perspectives

Avapritinib is effective and generally well tolerated

Submissions from UK Mastocytosis Support Group and Leukaemia Care
Technical engagement involved individual patient input

- AdvSM significantly shortens life expectancy and causes considerable disability
    - Experience symptoms common to advanced haematologic disease and ongoing mast cell degranulation as well as anaphylaxis
- Considerable unmet need as current treatments are not curative, do not manage all symptoms, and can cause significant side effects
- Very few patients available for research in each treatment pathway
- People who have had access to avapritinib report improved quality of life with minimal side effects
- People with AdvSM who have had both avapritinib and midostaurin prefer avapritinib as it does not cause vomiting, improves quality of life and has durable positive effects

"Unable to stay away from home for even a short period because of the unpredictability of my digestive system"

"…we have had to change everything we do, from what time we can go out in the morning (due to having to wait for my **post midostaurin nausea** to pass)…"

"Avapritinib restored every fibre of my being … stopped the repeated hospital admissions…8 episodes of anaphylaxis over nine weeks"

Clinical perspectives

Novel treatment for a rare fatal illness with high disease burden

Submissions from British Society of Allergy and Clinical Immunology

Clinical expert submissions also received at technical engagement

- AdvSM is a rare condition that requires management in specialist centres
- Extremely heterogeneous disease, can present in a variety of ways
- Limited effective therapeutic options available
- Main aim of treatment is to prevent disease progression, improve morbidity, increase overall survival and improve quality of life
- Avapritinib provides improved symptomatic control compared to midostaurin
- People with AdvSM experience better quality of life on avapritinib
- Studies indicate good tolerance and side effect profile for avapritinib

"…step-change in management of AdvSM in that it seems to provide deeper and more durable responses for the AdvSM such that the AHN often has a greater impact in determining prognosis."

"…avapritinib as a treatment option would, I believe, significantly improve pathway of care for patients with AdvSM"

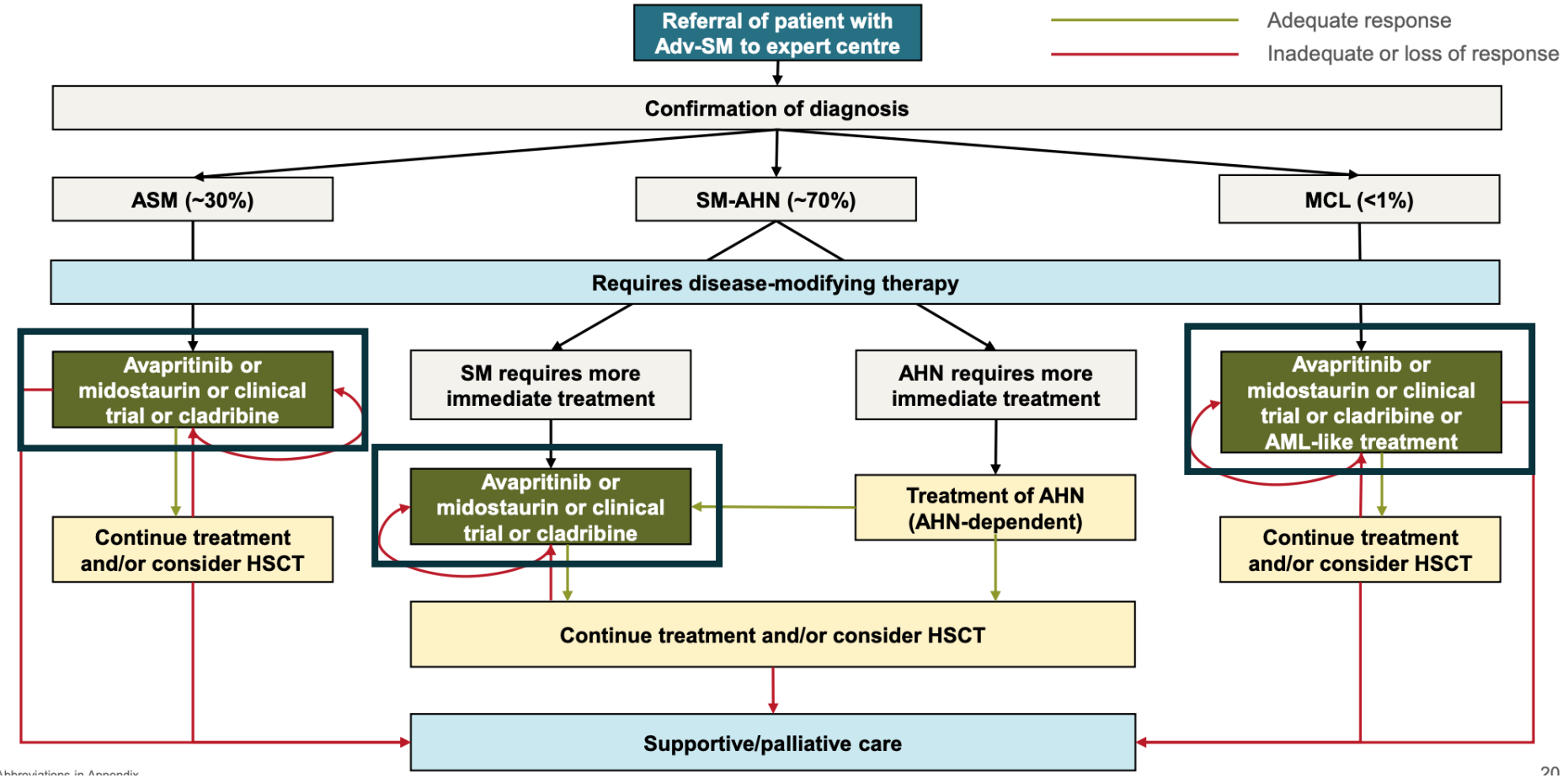
Equality considerations

No equality issues noted

- Company do not anticipate issues for people protected by equality legislation
- Avapritinib does not contain gelatine as an excipient, unlike midostaurin
  - Inclusion of gelatine can be problematic for people with certain religious or cultural beliefs
  - Clinical advice to the EAG (expert works at a centre with a multicultural patient population), had not experienced anyone not wishing to accept midostaurin treatment because it contains gelatine
  - This issue is unlikely to impact a large proportion people with AdvSM in NHS practice

Treatment pathway

Current treatment pathway for AdvSM, based on UK clinical expert advice



- Midostaurin is only therapy specifically indicated for AdvSM
- Company state avapritinib to be used mainly at 1L, but could also replace cladribine at 2L
- Considered before midostaurin due to increased potency and improved tolerability profile
- EAG: generally reflective of current NHS practice

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Figure 6, CS. AHN, associated haematological neoplasm; ASM, aggressive systemic mastocytosis; HSCT, haematopoietic stem cell transplant; MCL, mast cell leukaemia; SM, systemic mastocytosis

Avapritinib (Ayvakyt, Blueprint Medicines)

Marketing authorisation	• Avapritinib is anticipated to be indicated for the treatment of [redacted] • Type II variation via the national procedure was submitted to the MHRA on [redacted]. Anticipated date of GB marketing authorisation is [redacted]
Mechanism of action	• Type 1 tyrosine kinase inhibitor against *KIT* D816V variant protein • Bind and inhibit the active conformation of kinase receptors responsible for the majority of AdvSM cases • Prevents activation of downstream signalling pathways and uncontrolled mast cell activation and proliferation
Administration	• Recommended starting dose: 200mg orally once daily • Dose should be adjusted based on safety and tolerability • First reduction: 100mg, second reduction: 50mg, third reduction: 25mg
Price	• List price 25mg, 50mg, 100mg or 200mg tablets (30 tablets): £26,667 • Average cost per person per year: £324,448.50 • Simple discount PAS submitted to NHS England

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Table 2, CS. AdvSM, advanced systemic mastocytosis; AHN, associated haematological neoplasm; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM, systemic mastocytosis

Key issues

Issue		Resolved at TE?	ICER impact
1.	Lack of clarity of what constitutes “best available therapy” at second or subsequent lines	Yes	-
2.	Separation of the population by treatment line	No	Unknown
3.	Limitations of the effectiveness evidence	Partially resolved	Unknown
4.	Limitations of the indirect treatment comparisons	Partially resolved	Unknown
5.	Lack of consistency in the source of evidence used to inform the different survival parameters in the model	Yes	-
6.	Immaturity of the overall survival data used in the extrapolations	No	Large
7.	Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS	Partially resolved	Large
8.	Source of evidence used to inform time on treatment in the model	Yes	-
9.	Uncertain duration of treatment benefit for avapritinib	No	Large
10.	Exclusion of subsequent therapy costs	No	Unknown
11.	Uncertainty in the progression-free and progressive disease health state utility values	No	Small

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Key clinical trials PATHFINDER still ongoing

	PATHFINDER (n=107)	EXPLORER (n=86)	External control study (n=141)
Design	Phase 2, international, multicentre, open-label, single-arm	Phase 1, open-label, dose-finding, single-arm	Multicentre, observational, retrospective chart review
Population	Adults with AdvSM	Adults with AdvSM (n=69) and other myeloid malignancies (n=17)	Adults with AdvSM
Intervention	AVA 100/200mg, once daily (starting dose 200mg, n=105)	AVA 30-400mg, once daily (starting dose 200mg, n=20)	Non-interventional study
Comparator(s)	None	None	N/A
Primary outcome	Objective response rate	Max tolerated dose, AEs	OS
Key secondary outcomes	OS, PFS, response rate, symptom severity, AEs, HRQoL, measures of mast cell burden, DOR, TTR		DOT
Locations	US, UK, Europe, Canada	US, UK	US, UK, Europe
Used in model?	Yes	Yes	Yes

NICE Table 5, CS. AdvSM, advanced systemic mastocytosis; AE, adverse effects; AVA, avapritinib; DOR, duration of response; DOT, duration of treatment; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; TTR, time to response

Study data cuts

Latest data cut provided at technical engagement; limited time for EAG critique

	Submission: February 2024	Clarification: March 2024	Technical engagement: June 2024
PATHFINDER			
Data provided	September ‘22	Sept ‘23 requested: to be ‘provided at later date’	September ‘23
EXPLORER			
Data provided	April ‘22	Mix of April ’22/Jan ‘23	-
PATHFINDER/EXPLORER POOLED			
Data provided	April ’21/April ‘21	Sept ‘23/Jan ‘23 to be ‘provided at later date’	Sept’ 23/Jan ’23 **- Presented in clinical effectiveness, used in ITC** **- Used in economic model**

Sources: table 6, CS; company response to clarification; company response to technical engagement, page 6

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ITC, indirect treatment comparison

Key clinical trial results – PATHFINDER/EXPLORER, avapritinib

Overall survival – Sept/Jan 2023, submitted at TE

Figure 2, company addendum at TE

OS at 24months (all AdvSM)	[redacted]% (95% CI: [redacted]%, [redacted]%)

ASM: aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with associated haematological neoplasm; AdvSM; advanced systemic mastocytosis

Key clinical trial results – PATHFINDER/EXPLORER, avapritinib

Progression-free survival – Sept/Jan 2023, submitted at TE

Figure 6, company addendum at TE

Median PFS	[redacted] (95% CI: [redacted], [redacted])

ASM: aggressive systemic mastocytosis; MCL, mast cell leukaemia; SM-AHN, systemic mastocytosis with associated haematological neoplasm; AdvSM; advanced systemic mastocytosis

Key clinical trial results – PATHFINDER/EXPLORER, avapritinib

Survival by line of therapy*, Sept/Jan 2023, submitted at TE

OS

Figure 4, company addendum at TE

Red: prior systemic therapy (2L)
Blue: no prior systemic therapy (1L)

PFS

Figure 8, company addendum at TE

*prior systemic therapy: ~80% of people who had prior systemic therapy in the trial had prior midostaurin

Key issue 2: Separation of population by treatment line

Not resolved

Background

- Company separated population by treatment line, comparing with midostaurin 1L and cladribine 2L
- EAG considered limited justification; NICE recommendation for midostaurin (TA728) is not restricted to 1L
  - Also, cladribine likely used as subsequent treatment after either midostaurin or avapritinib

Company

- Did not change their position following technical engagement, provided no new evidence to address issue
- Should be separated; midostaurin well-defined as 1L option, cladribine most appropriate comparator for 2L

EAG comments

- Should be assessed compared with midostaurin in overall population; [redacted] and TA728 is not restricted to 1L population setting only
- While majority of people likely to be treated with midostaurin 1L, some will receive it 2L
- Assessing in overall population would also avoid discarding clinical effectiveness data by prior use of systemic therapies; happens when splitting the data by treatment line

Clinical and patient experts

- Avapritinib and midostaurin would be used 1L and 2L, with other treatments being used in subsequent lines

Should the avapritinib population be split according to treatment line?

1L, first line; 2L, second line

Partially resolved

Key issue 3: Limitations of the effectiveness evidence

Background

- Efficacy and safety of avapritinib based on 2 single-arm studies; PATHFINDER and EXPLORER
- PATHFINDER only analysis from Sept 2022, pooled analysis from both studies using data from 2020/2021
- EAG flagged data immaturity as an issue, and requested later data cuts to reduce uncertainty in OS/PFS

Company

- Provided updated effectiveness data at technical engagement in June 2024 (provided PATHFINDER Sept 2023 data cut, and PATHFINDER/EXPLORER Sept/Jan 2023 data cut)
- PATHFINDER response rates consistent with previous data cut offs, pooled response rates slightly lower

EAG comments

- [redacted] in PFS estimates between PATHFINDER 2022 and 2023 data cut offs as [redacted]; results in [redacted] PFS estimate from 2023 data cut off
- Updated data cut-offs reduced uncertainty in PFS estimates, but not OS estimates (median OS still not reached in majority of analysed populations)
- Lack of comparative clinical trials of avapritinib versus midostaurin or cladribine still a limitation

Clinical and patient experts

- AdvSM is extremely rare; evidence presented in current trials most robust in terms of safety and efficacy

Is the clinical effectiveness evidence appropriate for decision making?

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AdvSM, advanced systemic mastocytosis; PFS, progression-free survival; OS, overall survival

Indirect treatment comparison

IPTW determined as preferred method of ITC by company and EAG

- Company preferred inverse probability of treatment-weighted analysis (IPTW) using individual participant data from external control study; analyses provides most robust source of comparative evidence
  - Pooled results from PATHFINDER and EXPLORER compared to midostaurin and cladribine individually, across all lines of therapy
  - Initially used data from 2021/2022; EAG flagged this as a concern
    - Company updated at TE to include Sept 2023 (PATHFINDER) and Jan 2023 (EXPLORER) data

	Vs 1L midostaurin		Vs 2L+ cladribine	
	Unweighted	IPTW-weighted	Unweighted	IPTW-weighted
Median OS	[redacted] months ([redacted]) vs [redacted] months ([redacted])	[redacted] months ([redacted]) vs [redacted] months ([redacted])	[redacted] months ([redacted]) vs [redacted] months ([redacted])	[redacted] months ([redacted]) vs [redacted] months ([redacted])
HR	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])	[redacted] ([redacted])

tables 16 and 17, company addendum at TE

1L, first line; 2L+, second line; ITC, indirect treatment comparison; HR, hazard ratio; NE, not evaluable; NR, not reached; OS, overall survival

Key issue 4: Limitations of ITC

Partially resolved

Background

- EAG: IPTW most appropriate ITC, however, have concerns with adjustment for baseline characteristics
  - No adjustment for key prognostic variables (C-findings, bone marrow mast-cell burden, KIT D816V)
  - Over-adjustment for variables that may not be prognostic (region)
- Lack of details on methodology of adjustments, unable to see how well the adjusted populations matched

Company

- Provided additional details on methods of adjustment in IPTW at technical engagement
- Some not collected in routine practice; not available for use within ECS, and >90% had KIT mutation
- Region included due to differences in treatment availability/healthcare practices; could impact outcomes

EAG comments

- Company's analysis does not meet key assumptions of IPTW methods (no unmeasured confounders)
  - Potentially prognostic variables not collected in ECS could impact direction or magnitude of effect
- Difficult to ascertain reliability of findings of ITCs; still consider there to be uncertainties in IPTW

Clinical and patient experts

- Indirect comparisons less definitive than trials, but still of interest, especially in such a rare disease

Are the results of the indirect treatment comparison suitable for decision making?

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ECS, external control study; IPTW, inverse probability of treatment-weighted analysis; ITC, indirect treatment comparison

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Company's model overview

Partitioned survival model with three mutually exclusive health states, consistent with TA728

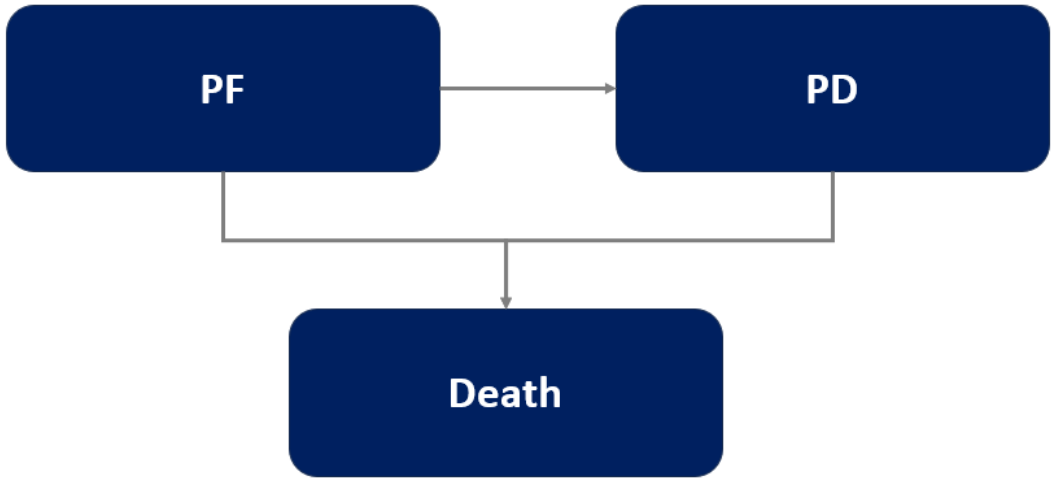

Figure 26, company submission

State	Definition
Progression-free	Alive, stable disease, and either exposed to primary treatment or switched to post-discontinuation
Progressed disease	Alive, experiencing worsening of disease, and either continuing primary treatment or on post-progression treatment
Death	Dead

- Technology modelled to affect QALYs by:
  - Increasing progression free survival
  - Increasing overall survival
  - Allowing proportion of avapritinib arm to discontinue treatment before disease progression
  - Applying a 7.5-year treatment benefit
- Technology modelled to affect costs by:
  - Increasing time on treatment, with associated drug acquisition and adverse event costs
  - Increasing size of progression-free cohort, with associated resource use consumption
  - Decreasing size of progressed-disease cohort, and need for palliative care at end of life

PD, progressed disease; PF, progression-free

Not resolved

Key issue 6: Immaturity of OS data used in extrapolations

Background

- Company's base case analysis used immature PATHFINDER 2022 OS data; median OS not reached

Company

- Company's updated pooled PATHFINDER/EXPLORER 2023 data provides additional 12 months follow-up
- However, median OS has not yet been reached in updated data cut in PATHFINDER 2023

EAG comments

- Findings from EXPLORER 2023 consistent with PATHFINDER 2023, but OS estimates from pooled data lower than PATHFINDER 2022
- Company's updated base case extrapolations predict [redacted] and [redacted] alive at 24 months for 1L and 2L+; higher than corresponding estimates of [redacted] and [redacted] from pooled PATHFINDER/EXPLORER 2023
- Extrapolated OS data beyond follow up of PATHFINDER/EXPLORER 2023 using different parametric functions leads to very different long-term survival outcomes; also dependent on treatment benefit duration

Clinical and patient experts

- OS data remains stable; consistent with what patients report

What are the committee's preferred assumptions for the long-term extrapolation of avapritinib?

1L, first line; 2L+, second line; OS, overall survival

Survival curves; overall survival, 1L, from TE

Overall survival, 1L avapritinib

Pooled PATHFINDER 2023 and EXPLORER 2023 data, 200mg dose

- Generalised gamma best fitting distribution for OS, followed by exponential and Gompertz
- Generalised gamma used in the model

Overall survival, 1L midostaurin

IPTW ECS analysis of pooled PATHFINDER 2023 and EXPLORER 2023

- Exponential best fitting distribution for OS, followed by log-normal and gamma
- Exponential used in the model

Incremental costs and QALYs for the comparison of avapritinib with 1L midostaurin are highly sensitive to the parametric extrapolation and the time on treatment benefit

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AIC, Akaike information criterion; BIC, Bayesian information criterion; TE, technical engagement

Survival curves; overall survival, 2L+, from TE

Overall survival, 2L avapritinib

Pooled PATHFINDER 2023 and EXPLORER 2023 data, 200mg dose

- Exponential best fitting distribution for OS, followed by log-normal and log-logistic
- Exponential used in the model

Overall survival, 2L+ cladribine

IPTW ECS analysis of pooled PATHFINDER 2023 and EXPLORER 2023

- Log-normal best fitting distribution for OS, followed by log-logistic and Gompertz
- Log-normal used in the model

Incremental costs and QALYs for the comparison of avapritinib with 2L+ cladribine are highly sensitive to the joint parametric extrapolations used for OS and TOT

NICE

AIC, Akaike information criterion; BIC, Bayesian information criterion; TE, technical engagement

Partially resolved

Key issue 7: Limited availability of PFS data and use of time on treatment (TOT) as a proxy for PFS

Background

- PFS not available from ECS to enable an IPTW comparison with PATHFINDER
- Company used comparator's TOT curve as proxy for PFS curve, but not for avapritinib
- EAG concerned about PFS data for avapritinib; RAC-RE population (unweighted analysis) of PATHFINDER inconsistent with OS data from the safety population (IPTW sample) of PATHFINDER

Company

- Company provided updated PFS estimates from pooled PATHFINDER and EXPLORER 2023 at technical engagement; reached median PFS of [redacted] months and [redacted] months in 1L and 2L+ respectively

EAG comments

- Findings from [redacted] for PFS; additional 12 months of follow-up data from PATHFINDER results in [redacted] PFS in 1L setting
- Pooled PATHFINDER/EXPLORER 2023 PFS data has alleviated concern about immaturity; however, uncertainty about long-term PFS remains
- As with OS, different parametric functions impact on cost-effectiveness results; also dependent on treatment benefit duration
- No alternative for TOT as proxy for comparator arm; but have now used more appropriate source for TOT

What is the committee's view on the level of uncertainty in the PFS data?

1L, first line; 2L+, second line; ECS, external control study; IPTW, inverse probability of treatment-weighted analysis; OS, overall survival; PFS, progression-free survival; RAC-RE, response-evaluable; TOT, time on treatment

Not resolved

Key issue 9: Uncertain duration of treatment benefit

Background

- Treatment benefit duration for avapritinib assumed to be 5yrs in company's original submission, based on rate of duration of response in PATHFINDER 2022 (70.5% at 42 months) in AdvSM RAC-RE population
- EAG considered 5yrs reasonable in 1L; but could be pessimistic - ~[redacted]% of people still on treatment at 5yrs

Company

- In updated base case, noted that pooled ECS IPTW analysis to inform TOT resulted in greater proportion of people remaining on treatment at 7.5yrs ([redacted]% vs [redacted]% in original base case 1L, [redacted]% vs [redacted]% 2L+)
- Updated treatment benefit assumption to 7.5yrs, in line with expectations of consultant haematologists

EAG comments

- If more sustained disease response is achieved while people receive avapritinib, revised treatment benefit of 7.5yrs reasonable in light of longer duration of treatment in updated pooled analysis
- Duration of treatment benefit shouldn't be considered in isolation of survival outcomes; incremental costs and QALYs highly sensitive to different parametric survival extrapolations
- Provided scenario analysis assessing alternative duration/size treatment effect with different extrapolations

Clinical and patient experts

- Treatment benefit of 5 to 7 years reasonable

What duration of treatment benefit is most reasonable?

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1L, first line; 2L+, second line; ECS, external control study; IPTW, inverse probability of treatment-weighted analysis; RAC-RE, response-evaluable; TOT, time on treatment

Key issue 10: Exclusion of subsequent therapy costs

Not resolved

Background

- Impact of subsequent therapy use on survival outcomes after discontinuation from initial treatment not considered in company's original base case in 1L or 2L+
- EAG: concern of potential confounding of subsequent treatment effects, but costs (and utility values) associated with use of subsequent therapies excluded from model, particularly in relation to allo-HSCT

Company

- No data on subsequent treatment use and post-progression survival outcomes to inform model
- Feedback from consultant haematologists: subsequent treatments after avapritinib 1L include cladribine (30-35%) and AML-like treatments (50%)

EAG comments

- Remain concerned about potential confounding of subsequent treatment effects on survival outcomes reported in updated pooled PATHFINDER/EXPLORER 2023 data for proportion of cohort who received allo-HSCT post-avapritinib discontinuation
- No information on treatments used post-avapritinib reported

Clinical and patient experts

- Option of allo-HSCT not available to many patients; dictated by disease status
  - High risk mutations, age, comorbidities, availability of potential donors

Should costs associated with subsequent therapies be included in the cost-effectiveness analysis?

1L, first line; 2L+, second line; allo-HSCT, allogenic haematopoietic stem cell transplant; AML, acute myeloid leukaemia

Not resolved

Key issue 11: Uncertainty in the progression-free and progressive disease health state utility values

Background

- EAG noted uncertainty in utility values for progression-free and progressed-disease health states
  - Limited number of observations to inform mapped utility values, and PD/PF utility for deriving PD utility
  - Generalisability of AML utilities to AdvSM, large variability, mean age lower than modelled population

Company

- At TE, provided updated health state utility values using pooled PATHFINDER/EXPLORER 2023 data

EAG comments

- Company haven't provided details on number of additional observations used to inform updated PF value
- Concerns raised relating to PD/PF utility ratio remain as methodology has not changed
- QALYs highly sensitive to utility values used in model

Health state	Original company base case utility value	Updated company base case utility value
PF (1L)	[redacted]	[redacted]
PD (1L)	[redacted]	[redacted]
PF (2L+)	[redacted]	[redacted]
PD (2L+)	[redacted]	[redacted]

Clinical and patient experts

- Quality of life seriously impacted by disease; align with patient experiences of different health states

Are the utility values for PF and PD health states realistic?

1L, first line; 2L+, second line; AdvSM, advanced systemic mastocytosis; AML, acute myeloid leukaemia; PD, progressed disease; PF, progression-free; TE, technical engagement; TLR, targeted literature review

QALY weightings for severity

Background

- Severity considered in analysis provided pre-technical engagement, applied for 2L+ population
- Updated analysis provided at technical engagement; severity not considered by company
- EAG confirmed severity weighting no longer holds for either 1L or 2L+ population with new data-cut provided at technical engagement, and the company's new cost-effectiveness analyses where the EAG's preferred assumptions have been accepted

Table 6.1, NICE health technology evaluations: the manual

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
x1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	Absolute QALY shortfall*	Proportional QALY shortfall**
Company base case: 1L Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]
Company base case: 2L+ Cladribine	[redacted]	[redacted]	[redacted]	[redacted]

1L, first line; 2L+, second line

Summary of company and EAG base case assumptions

EAG preferred base case matches company base case post technical engagement, as company have accepted EAG's preferred assumptions

Assumptions in company and EAG base case (table 4, company TE response)

Assumption	Company base case	EAG base case
Overall survival source	Pooled PATHFINDER and EXPLORER 2023 ECS IPTW	
Overall survival extrapolation, 1L	Avapritinib: generalised gamma Midostaurin: exponential	
Overall survival extrapolation, 2L	Avapritinib: exponential Cladribine: log-normal	
Progression free survival source	Pooled PATHFINDER and EXPLORER 2023 RAC-RE population	
Utility: PF HRQoL	Pooled PATHFINDER and EXPLORER 2023	
Adverse events	Pooled PATHFINDER and EXPLORER 2023	
Duration of treatment benefit	7.5 years	

1L, first-line; 2L, second line; ECS, external control study; HRQoL, health-related quality of life; IPTW, inverse probability of treatment weighting; PF, progression-free; RAC-RE, response-evaluable

Key issues

Issue		Resolved at TE?	ICER impact
1.	Lack of clarity of what constitutes “best available therapy” at second or subsequent lines	Yes	-
2.	Separation of the population by treatment line	No	Unknown
3.	Limitations of the effectiveness evidence	Partially resolved	Unknown
4.	Limitations of the indirect treatment comparisons	Partially resolved	Unknown
5.	Lack of consistency in the source of evidence used to inform the different survival parameters in the model	Yes	-
6.	Immaturity of the overall survival data used in the extrapolations	No	Large
7.	Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS	Partially resolved	Large
8.	Source of evidence used to inform time on treatment in the model	Yes	-
9.	Uncertain duration of treatment benefit for avapritinib	No	Large
10.	Exclusion of subsequent therapy costs	No	Unknown
11.	Uncertainty in the progression-free and progressive disease health state utility values	No	Small

Cost-effectiveness results, and scenarios to consider

- **All ICERs >£30,000**

In Part 2, the committee will consider a range of scenarios (including scenario combinations in some circumstances):

- Optimistic and pessimistic OS extrapolations for avapritinib and midostaurin (1L) or cladribine (2L)
- Optimistic and pessimistic TOT extrapolations for avapritinib and midostaurin (1L) or cladribine (2L)
- Duration of treatment effect of 5 years, 7.5 years, 10 years and lifetime
- EAG base case + PF utility of 0.7 (midostaurin) or 0.6 (cladribine)

1L, first time; 2L, second line; OS, overall survival; PF, progression-free; TOT, time on treatment

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

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Key issues

Issue		Resolved at TE?	ICER impact
1.	Lack of clarity of what constitutes “best available therapy” at second or subsequent lines	Yes	-
2.	Separation of the population by treatment line	No	Unknown
3.	Limitations of the effectiveness evidence	Partially resolved	Unknown
4.	Limitations of the indirect treatment comparisons	Partially resolved	Unknown
5.	Lack of consistency in the source of evidence used to inform the different survival parameters in the model	Yes	-
6.	Immaturity of the overall survival data used in the extrapolations	No	Large
7.	Limited availability of progression-free survival (PFS) data and use of time on treatment as a proxy for PFS	Partially resolved	Large
8.	Source of evidence used to inform time on treatment in the model	Yes	-
9.	Uncertain duration of treatment benefit for avapritinib	No	Large
10.	Exclusion of subsequent therapy costs	No	Unknown
11.	Uncertainty in the progression-free and progressive disease health state utility values	No	Small

Avapritinib for treating advanced systemic mastocytosis [ID3770]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Unweighted analysis from IPTW using ECS – overall survival

Avapritinib improves OS vs 1L midostaurin and 2L+ cladribine

vs midostaurin, figure 11, company addendum at TE

vs cladribine, figure 12, company addendum at TE

Unweighted	Vs 1L midostaurin	Vs 2L+ cladribine
Median OS	[redacted] ([redacted], [redacted]) vs [redacted] months ([redacted], [redacted])	[redacted] ([redacted], [redacted]) vs [redacted] months ([redacted], [redacted])
HR	[redacted] ([redacted], [redacted]; [redacted])	[redacted] ([redacted], [redacted]; [redacted])

1L, first line; 2L+, second line; HR, hazard ratio; NE, not evaluable; OS, overall survival

AIC/BIC data from survival curves

Overall survival, 1L avapritinib

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
AIC + BIC	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall survival, 1L midostaurin

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall survival, 2L+ avapritinib

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall survival, 2L+ cladribine

	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma	Gamma
AIC + BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; TE, technical engagement

Survival curves; company's base case analysis

Overall survival, progression-free survival, time on treatment vs 1L midostaurin

figure 8, EAG response to TE

Survival curves; company's base case analysis

Overall survival, progression-free survival, time on treatment vs 2L+ cladribine

figure 9, EAG response to TE

Survival curves; PFS, 1L, from TE

Pooled PATHFINDER 2023 and EXPLORER 2023 data, 200mg dose

- Exponential best fitting distribution for PFS, used in company base case

Health state utility values

EQ-5D data not available from PATHFINDER or EXPLORER

- EORTC QLQ-C30 from RAC-RE population of PATHFINDER mapped onto EQ-5D-3L using algorithm by Young et al., (2015)
- Mapped utility values for each individual across all observations prior to progression averaged to derive a single utility value for PF state
- Only one observation for the PD state, even after pooling PATHFINDER and EXPLORER, therefore company used literature to identify relevant health state utility value for post-progression in AdvSM
    - Six studies were identified, four used to calculate a ratio between PD and PF utility values
        - Large variation in the ratios ([redacted]) and mean age (44.3 to 60 years)
        - All four studies included patients with AML
    - Weighted average of the ratios in each study derived ([redacted]), and applied to PF utility values for 1L and 2L+ populations to estimate utility value for PD health state, for each population separately
- Utility values were adjusted for ageing in model, and values were not permitted to exceed gender and age-adjusted UK general population norms
- Disutilities associated with grade 3+ adverse events are included in model

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AML, acute myeloid leukaemia; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire; PD, progressed disease; PF, progression-free; TLR, targeted literature review