NICE National Institute for Health and Care Excellence

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OBSERVER HANDOUTS

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours

Lead team presentation

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Company: Blueprint Medicines

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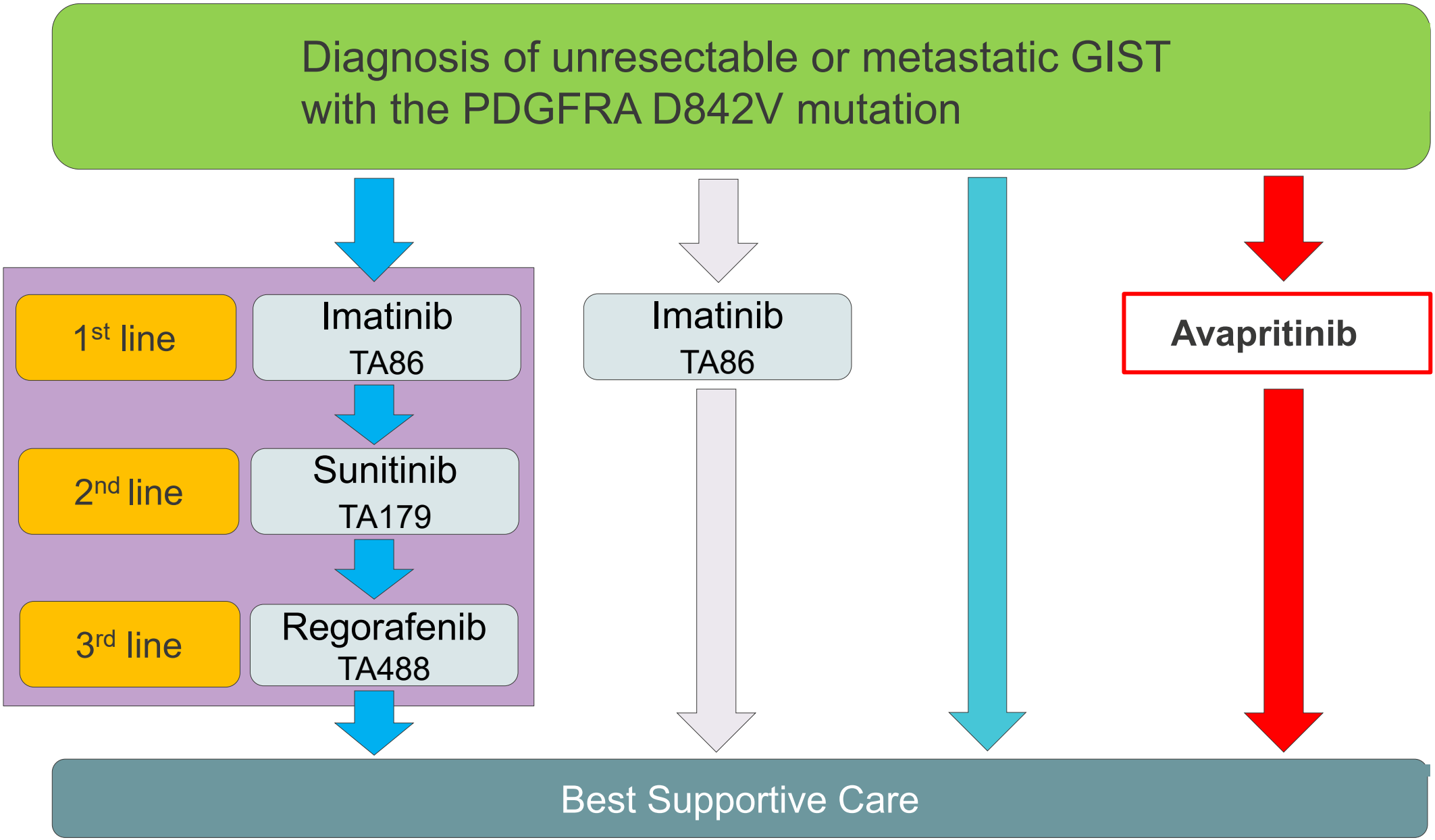
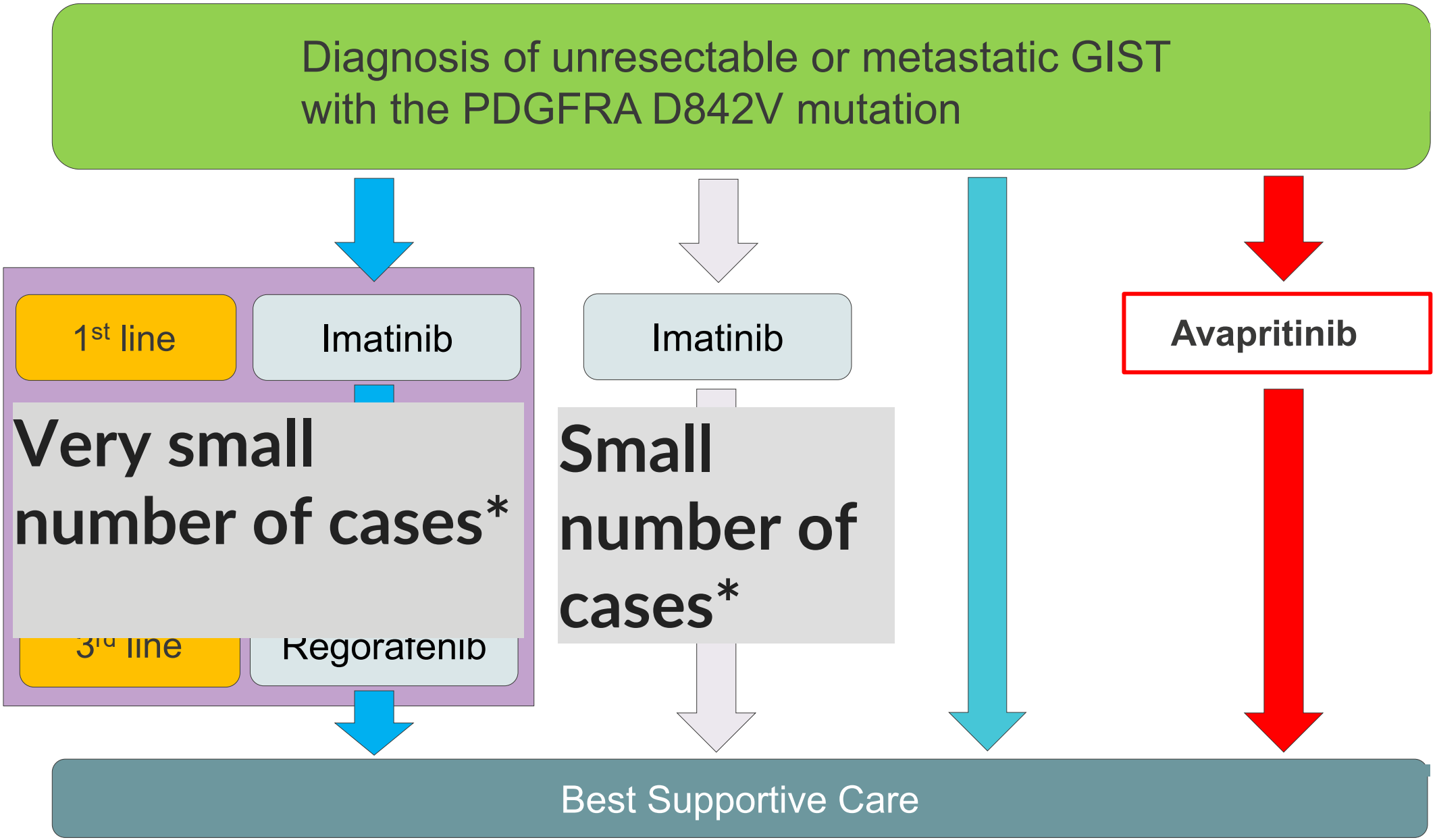
Key issues

Issue 1.	Treatment pathway in economic model
Issue 2.	Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs
Issue 3.	Modelling time on treatment
Issue 4.	Extrapolation of overall survival
Issue 5.	Extrapolation of progression-free survival for 2nd and 3rd line established clinical management (ECM) treatments
Issue 6.	Treatment effect duration
Issue 7.	Utility values in the economic model
Issue 8.	End of life criteria
Issue 10. NEW	Treatment dosing pattern scenario in the updated economic model
Issue 11. NEW	Dose reduction and drug wastage
Issue 9.	Cancer Drugs Fund

Treatment Pathway



Treatment Pathway



*based on clinical expert opinion and comments received through technical engagement.

Avapritinib (Blueprint medicines)

Mechanism	Avapritinib is a Type 1 tyrosine kinase inhibitor that selectively inhibits the activity of the tyrosine-protein kinase KIT, CD117 (KIT) and platelet-derived growth factor receptor alpha (PDGFRA) genes.
Marketing authorisation	On 24 September 2020 the European Medicines Agency granted conditional marketing authorisation for avapritinib
Anticipated market authorisation wording	"..as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation"
Administration and dose	Avapritinib is given orally as a 300 mg tablet, once daily. The dose should be adjusted based on safety and efficacy. Treatment should be continued until disease progression or unacceptable toxicity.
Indicative list price	£26,666.67 for 30 tablets (100 mg, 200 mg or 300 mg)

Background

Comparators	Established clinical management & best supportive care
Main clinical trials	**NAVIGATOR:** Phase I/II, open label, single arm, **BLU-285-1002:** Retrospective chart review
Key results	**NAVIGATOR: (avapritinib given as 1st, 2nd, 3rd or 4th line therapy)** • Median overall survival = Not reached • Median progression-free survival = 29.2 [redacted] • **BLU-285-1002: (company-sponsored retrospective chart review of ECM)** • Median overall survival = [redacted] • Median overall survival = [redacted] • Median progression-free survival = [redacted] • Median progression-free survival = [redacted]
Comparison with ECM	Adjusted indirect treatment comparison (ITC) between 2 single-arm studies: NAVIGATOR and BLU-285-1002 for avapritinib and established clinical management (ECM)
Key result	OS hazard ratio for ECM vs avapritinib = [redacted] PFS hazard ratio for ECM vs avapritinib = [redacted]
Model	Cohort partitioned survival
Company base-case ICER	£49,996 per QALY gained

NAVIGATOR clinical results (PDGFRA mutant GIST population subset* (n=56)

Outcome	
Overall response, n (%) [95% confidence interval]	[redacted]
Median duration of response, months (95% confidence interval [CI])	[redacted]
Median overall survival, months (95% CI)	Not reached
Median progression-free survival, months (95% CI)	29.2 [redacted]
Median time to response (days)	[redacted]
Median time on treatment, months (95% CI)	[redacted]
Health-related quality of life	Not reported

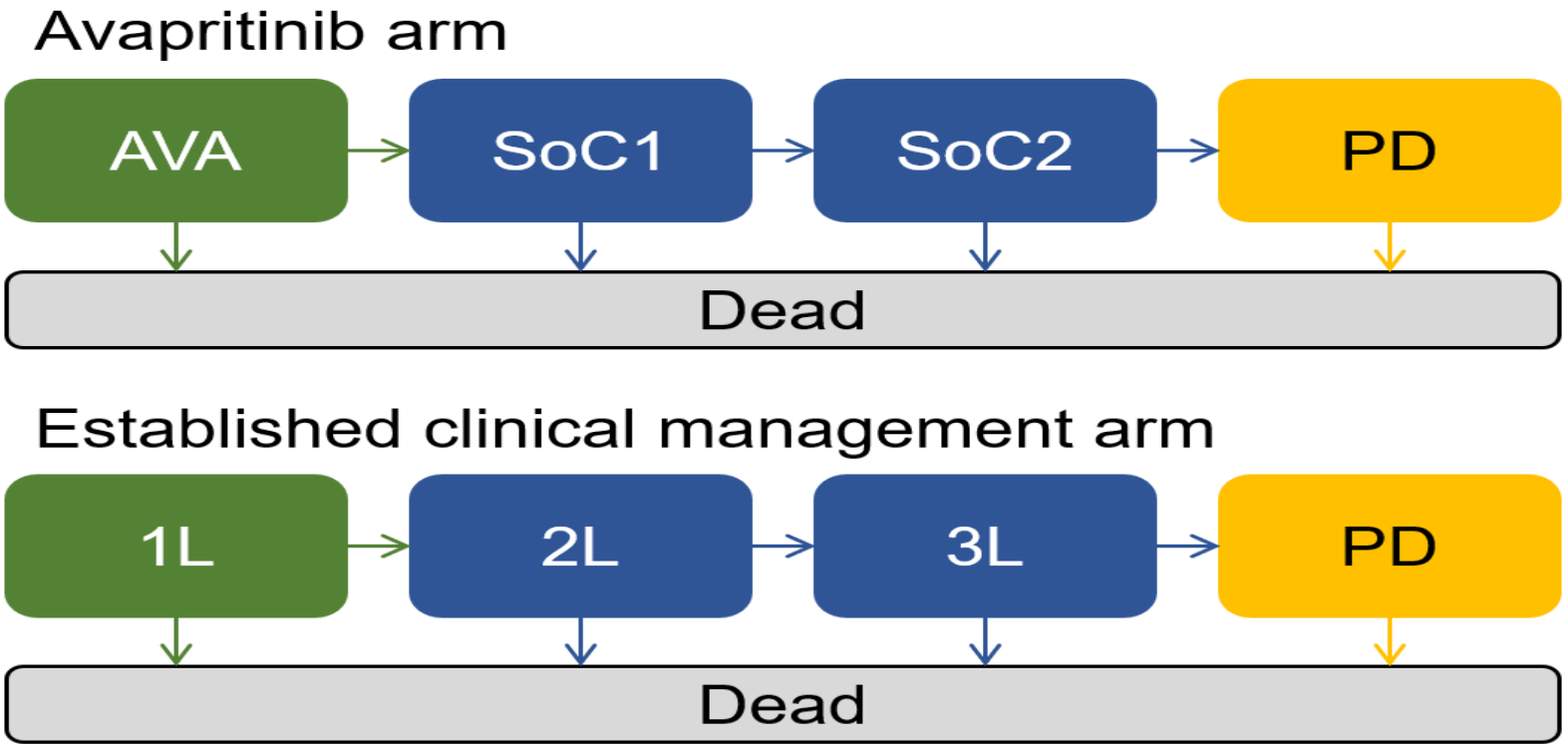
*[redacted]

BLU-285-1002 clinical results for ECM (PDGFRA mutant GIST population previously treated with TKI subset* (n=19)

Outcome	
Overall response, n (%)	[redacted]
Median duration of response (months)	Not reported
Median overall survival, months (95% confidence interval [CI])	[redacted]
Median progression-free survival, months (95% CI)	[redacted]
Median time to response (days)	Not reported
Median time on treatment (months)	Not reported
Health-related quality of life	Not reported

*[redacted]

Model structure



Key: 1L, first line; 2L, second line; 3L, third line; AVA, avapritinib; PD, progressive disease; SoC, standard of care.

Notes:

- *SoC1 and SoC2 differ from 2L and 3L only in terms of treatment cost. All other parameters are identical.*
- *Probability of transition from SoC1 to SoC2 same as probability of transition from 2L to 3L*
- *Probability of transition from SoC2 to PD same as probability of transition from 3L to PD*

Model assumptions

Time Horizon	40 years*
Treatment waning effect	5 years
Utility values	NICE Technology appraisals 86 (imatinib), 179 (sunitinib), 488 (regorafenib)
Costs and resource use	NICE Technology appraisals 86, 179, 488, updated with a survey conducted with 5 GIST medical oncologists in England and Wales
Cycle length	1 month
Half-cycle correction	Yes
Discounting	3.5% for costs and effects
Perspective	NHS/PSS

* **Note:** Patients enter the model at [redacted] years of age

Patient and carer perspectives

- GIST is the most common type of soft tissue sarcoma
- Whilst GIST patients can, on the whole, live normal lives, side effects of treatment can be debilitating
- Treatments are regularly ineffective - PDGRFA D842V-driven GIST. Increased number of kinder, more effective therapies would be welcomed
- Avapritinib is a precision medicine that targets PDGFRA mutations and is well tolerated
- Trials show dramatic and durable responses for GIST patients with PDGFRA
- PDGFRA mutated GIST patients do not have an effective treatment where surgery is not possible
- Avapritinib will reduce unnecessary expenditure on other ineffective therapies that are very expensive for the NHS.

Sources: Sarcoma UK & GIST Cancer UK submissions

Clinical expert statements

- Avapritinib: best example of precision medicine targeting PDGFRA gene mutations in GISTs
- Significant and dramatic responses observed in clinical trials
- Durable and significant improvement in progression free survival has been noted
- Well tolerated drug, however, requires careful clinical monitoring and should be used in specialist GIST/Sarcoma centres
- Avapritinib is paradigm changing in the subset of GISTs with PDGFRA D842V mutation.

Source: Clinical consultant submission

Issues resolved after technical engagement (1)

	Summary	Technical team consideration	Stakeholder responses	Updated company base case?
3	Time on treatment for avapritinib captured and extrapolated using Gompertz parametric model ERG base-case assumes ToT for avapritinib to be equal to PFS and prefer Weibull model for ECM arm of 2nd line and 3rd line treatments	The technical team agree with the ERG that the Weibull distribution curve should be applied for ToT because it is consistent with the technical teams preferred model used for PFS (see issue 5) and provides a better statistical fit to the observed data.	Company Although not convinced Weibull is able to incorporate complexity of a reducing hazard and model survival estimates, agree, reasonable to use a Weibull model in the interest of conservatism	Yes

Issues resolved after technical engagement (2)

	Summary	Technical team consideration	Stakeholder responses	Updated company base case?
5	Extrapolated PFS for each line of therapy using following distribution curves: • 1st line: avapritinib = Weibull, ECM (imatinib) = Weibull • 2nd line (sunitinib): Log-logistic • 3rd line (regorafenib): Gompertz ERG agree using Weibull for avapritinib and 1st line ECM (imatinib) For 2nd line ECM (sunitinib) and 3rd line ECM (regorafenib) disagree with company choice. Prefer Weibull distribution curve for both because consistent with the 1st line model and provides better statistical fit.	The technical team agree that the Weibull distribution curve should be applied to extrapolate PFS for 2nd and 3rd line treatments	Company Substantial uncertainty but agree ERG's approach is reasonable	Yes

Outstanding issues after technical engagement

Issue 1: Treatment pathway in economic model

Issue 2: Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKI's

Issue 4: Extrapolation of overall survival

Issue 6: Treatment effect duration

Issue 7: Utility values in the economic model

Issue 8: End of Life criteria

Issue 9 (New): Treatment dosing pattern in the updated economic model

Issue 11 (New): Dose reduction and drug wastage

Issue 10: Cancer Drugs Fund

Issue 1: Treatment pathway in economic model

Company submission:

Line of therapy	Intervention arm	Comparator arm (ECM)*
1st	avapritinib	imatinib
2nd	Standard of Care	sunitinib
3rd	Standard of Care	regorafenib

*ECM = Established Clinical Management

ERG comment:

- Uncertainty in clinical treatment pathway with proportions of PDGFRA D842V patients who would receive imatinib, sunitinib, regorafenib and/or best supportive care
- Company clinical studies: majority received prior tyrosine kinase inhibitors (TKIs) – In UK clinical practice would expect most people to receive best supportive care
- Patients in economic model are assumed to have had no previous TKIs unlike those in the NAVIGATOR and BLU-285-1002 studies. Clinical experts advising ERG agreed that few patients would receive TKIs in clinical practice
- ERG base-case assumption for proportion of patients receiving TKIs in ECM is 20% imatinib, 10% sunitinib, 10% regorafenib.

Issue 1: Treatment pathway in economic model

Company response from engagement:

- Believe ERG's market share adjustments do not accurately represent population
- Imatinib, sunitinib and regorafenib are recommended in clinical guidelines, as first-, second-, and third-line treatments for unresectable or metastatic GIST, regardless of mutation status so includes patients with PDGFRA D842V-mutated GIST
- Survey of clinical experts: most suggested TKIs used for treating unresectable or metastatic PDGFRA D842V GIST
- Although uncertainty remains - plausible to assume majority of patients in England receive imatinib, sunitinib and regorafenib at first-, second- and third-line, respectively.

ERG considerations on company engagement comments:

- 2 clinical expert advisors both agreed that few patients in ECM arm would receive these TKIs due to lack of efficacy, and those who do would mostly receive only imatinib
- Company do not explain why NICE guidance, which is for the general GIST population, should apply to patients with the PDGFRA D842V mutation in whom the TKIs lack efficacy
- Company's original submission states that the TKI treatments in the ECM arm have a lack of efficacy in this population with very low overall response rates - confirmed by company's clinical experts

Issue 1: Treatment pathway in economic model

NCRI-ACP-RCP-RCR & clinical expert comments:

- No standard treatments available - some treated with imatinib to see if symptomatic response achieved. No treatments standardly used beyond 1st line
- Estimate >50% of patients with advanced D842V GIST will have received imatinib but very few receive 2nd line or beyond
- Very few patients would be treated with standard 1st, 2nd or 3rd line treatments. Particularly as a compassionate use programme for avapritinib is currently available.
- Very small number of patients with D842V mutations may be undiagnosed and receive imatinib/sunitinib/regorafenib as per standard GIST paradigm
- Small number might be offered imatinib. Progression on imatinib - patients would be offered best supportive care or clinical trial if available.

Technical team judgement: Uncertainty remains but clinical expert comments suggest the treatment pathway used in the company's economic model does not reflect that used in clinical practice in the NHS in England.

KEY QUESTION: Does the treatment pathway in the economic model reflect that seen in the NHS in England?

Issue 2: Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs

Company submission: NAVIGATOR and BLU-285-1002 clinical studies allowed patients to receive TKIs prior to treatment with avapritinib or established clinical management (ECM)

ERG comment:

- Patients in NAVIGATOR study (receiving avapritinib) received more frequent prior TKI use than would be expected in UK clinical practice, despite TKIs being ineffective in the PDGFRA D842V subgroup
- TKI use is only reported for the full study population of BLU-285-1002, therefore would include adjuvant therapy for locally advanced disease, not specifically advanced/metastatic.

Company response from engagement:

- Data used have limitations but remain the best evidence available at present
- Avapritinib likely to be used first-line but not feasible to recruit sufficiently large sample of first-line patients into a clinical trial
- NAVIGATOR: [redacted]% of patients received prior treatment with imatinib, [redacted]% sunitinib and [redacted]% regorafenib. [redacted] ([redacted]%) had not received any prior TKI therapy
- True OS benefit likely underestimated - outcomes of patients treated at first-line likely to be better than at later lines, given ineffective nature of other TKIs. Also, patients receiving avapritinib at later treatment lines are less likely to benefit from post-discontinuation treatment effect.

Issue 2: Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs

ERG considerations on company engagement comments:

- Agree survival benefit of avapritinib likely underestimated (NAVIGATOR vs UK clinical practice)
- Generalisability of BLU-285-1002 study to UK practice is uncertain
- Agree earlier avapritinib treatment: possible better outcomes than after 1 or more TKIs. However, also note these patients may also spend more time on avapritinib (even if better survival with no prior TKIs = not necessarily follow an improvement in cost-effectiveness)

NCRI-ACP-RCP-RCR & clinical expert comments:

- Study populations broadly generalisable although more patients in other countries will have received more lines of therapy
- Treatment effect would be similar - those who have not received prior TKI may well be of better performance status but this is a generalisation
- Largely generalisable - probable that fewer patients in UK will have received prior TKI.

Technical team judgement: The population in the clinical trials is broadly generalisable to that seen in the NHS in England although uncertainty remains as to the use, and possible clinical effect, of having prior TKIs.

KEY QUESTION:

- *Are the populations in the clinical studies generalisable to the NHS in England?*

Issue 4: Extrapolation of overall survival

Company submission

Avapritinib arm	Established clinical management arm
Modelled OS using components of: • Pre-discontinuation mortality (NAVIGATOR) • Time on treatment (NAVIGATOR) • ECM survival (BLU-285-1002) • Assumption on treatment waning	Modelled OS using extrapolation of observations directly from BLU-285-1002
log-normal model to extrapolate	Weibull model to extrapolate
Censor NAVIGATOR OS for discontinuation events so captures mortality only for patients still receiving avapritinib	No censoring

ERG comment:

- Fitting OS to uncensored Kaplan-Meier data from the NAVIGATOR study is preferable
- Highlighted NICE DSU guidance 14 = same distribution appropriate for both treatment arms. So Weibull distribution should be used for both avapritinib and ECM. Changing distribution from log-normal to Weibull minimal effect on cost effectiveness results
- **Base case:** Used company model but corrected OS extrapolation by varying treatment waning duration (see issue 6). Weibull distribution for both avapritinib and ECM.

Issue 4: Extrapolation of overall survival

Company response from engagement:

- Experts consulted agreed that survival outcomes in the company base-case model were plausible for the population who would be treated with avapritinib and ECM in UK clinical practice
- ERG estimated survival at 5–11% and 0% at 5 and 10 years, respectively is lower than survival observed in Weibull extrapolation of the ECM arm Kaplan–Meier from BLU-285-1002.

ERG considerations on company engagement comments:

- Note company use a Weibull distribution to model OS for avapritinib in their updated analysis, as recommended by ERG

NCRI-ACP-RCP-RCR:

- Overall survival of patients with advanced D842V GIST is around 15 months according to published data.

Technical team judgement: The technical team requested that the company provide additional analyses using the full OS data from the NAVIGATOR study IPW analysis, uncensored for discontinuation.

Issue 4: Extrapolation of overall survival

Company response to additional analyses request:

- Simple extrapolation of OS provides a very conservative estimation of expected overall survival (estimated OS using log-logistic or log-normal extrapolation comparable to mean OS in ERG preferred base case)
- A post-discontinuation treatment effect should be reflected in the modelling
- Prognoses for patients treated at first-line would be better than those at later lines, meaning a mixed-lines OS KM is likely to be a considerable underestimate of overall survival in clinical practice
- First-line analysis should only be used for reference and not for decision making – considerable uncertainty and small sample size

ERG considerations on company's additional analyses:

- Analyses were appropriately implemented in the economic model
- Weibull distribution should be used for both avapritinib and ECM
- Agree OS and ICER for first-line not significantly different from those of overall PDGFRA cohort
- Agree results for first-line patients should be treated with caution, given the small sample size

Technical team judgement: The technical team preferred approach to extrapolation of OS is using the full OS data from the NAVIGATOR study IPW analysis that is uncensored for discontinuation.

KEY QUESTION: What is the most appropriate approach to extrapolation of OS?

Issue 4: Extrapolation of overall survival

Direct extrapolation of full uncensored OS IPW adjusted data from NAVIGATOR - March 2020 data cut

Fit Statistics	AIC	BIC
Exponential	115.18	117.21
Weibull	111.93	115.98
Gompertz	144.21	148.26
Log-normal	138.52	142.57
Log-logistic	139.81	143.86

Company: log-logistic or log-normal extrapolation should be used for decision making

Source: Company response to additional analyses request

Issue 4: Extrapolation of overall survival – 1st line

Direct extrapolation of uncensored OS NAVIGATOR IPW adjusted data for people who received first-line avapritinib (n=[redacted]) - March 2020 data cut

Fit Statistics	AIC	BIC
Exponential	33.10	33.80
Weibull	33.76	34.55
Gompertz	50.11	50.91
Log-normal	48.84	49.64
Log-logistic	49.05	49.85

Company: log-logistic or log-normal extrapolation should be used for decision making

Source: Company response to additional analyses request

Issue 4: Extrapolation of overall survival

Comparison of the OS estimates with and without censoring for discontinuation

Time	Updated base case model with OS censored for discontinuation, linked to ToT and extrapolated using Weibull		Updated model for additional analysis with OS uncensored for discontinuation; simple extrapolation using log-normal		Updated model for additional analysis with OS uncensored for discontinuation; simple extrapolation using Weibull	
	Avapritinib	ECM	Avapritinib	ECM	Avapritinib	ECM
1 year	[redacted]	45%	[redacted]	45%	[redacted]	45%
2 years	[redacted]	29%	[redacted]	29%	[redacted]	29%
3 years	[redacted]	20%	[redacted]	20%	[redacted]	20%
4 years	[redacted]	14%	[redacted]	14%	[redacted]	14%
5 years	[redacted]	11%	[redacted]	11%	[redacted]	11%

ECM: established clinical management; ToT: time on treatment

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Source: ERG response to additional analyses received from company

Issue 6: Treatment effect duration

Company model assumes: a gradual movement from avapritinib pre-discontinuation hazards to the OS hazards of the established clinical management (ECM) arm, after stopping treatment with avapritinib. This means a gradual loss of treatment effect over a period of 5 years (60 months).

ERG comment:

- Assumption of treatment benefit for 5 years after stopping avapritinib is not appropriate
- Risk of death for people discontinuing avapritinib would rapidly increase to a similar risk as the ECM arm - based on advice of clinical experts
- ERG base case = waning duration of 1 month (gives close fit to observed OS data).

Company response from engagement:

- Updated base-case assumes benefit after stopping treatment for 18 months rather than 60 - value slightly below midpoint between 2 recent TKI NICE appraisals, TA621 (osimertinib for untreated EGFR mutation-positive NSCLC) and TA463 (cabozantinib for previously treated advanced renal cell carcinoma)
- 18 month more plausible than 1 month in ERG base-case. 1 month assumption results in:
  - Worse survival outcome than simple extrapolation of NAVIGATOR Kaplan–Meier data
  - NAVIGATOR OS Kaplan–Meier likely to underestimate survival of patients receiving avapritinib in clinical practice - due to higher use of prior TKIs
  - Clinical testimony and evidence suggest that TKIs in general and avapritinib specifically have a post-discontinuation treatment effect lasting a considerable period of time.

Issue 6: Treatment effect duration

ERG considerations on company engagement comments:

- Note that the appraisals suggested (TA621 & TA463) are for different indications = uncertainty whether assumptions used in these appraisals are generalisable to current appraisal
- Agree that the post-discontinuation treatment effect duration would be considerably shorter than 60 months
- Rationale for choosing 1 month for duration of post-discontinuation effect is provides a better fit against the study K-M data. Choosing a longer post-discontinuation effect duration results in an overestimate of the OS for avapritinib compared to the study K-M data (**see next slide**)

NCRI-ACP-RCP-RCR & clinical expert comment:

- Currently there is no data in the public domain to support survival advantage 5 years after stopping treatment
- ERG's position of 1 month after stopping treatment is also not certain.

Technical team judgement: Uncertainty remains as to the true profile of treatment waning after stopping avapritinib.

KEY QUESTION: What is the most appropriate treatment effect duration?

Impact of different treatment effect durations

[redacted]

Key: AVA = avapritinib; ECM = established clinical management

Source: Company response to technical engagement

Issue 7: Utility values in the economic model

Company model:
Health-state utility values from previous unresectable or metastatic GIST appraisals (TA86, TA179, and TA488) used to capture HRQoL as move through treatment pathway (No data collected in NAVIGATOR, no EQ-5D-based or EQ-5D-mappable evidence specific to PDGFRA D842V-mutated GIST exists)

Summary of utility values for cost-effectiveness analysis

Progression-free survival	Utility value
1st line – avapritinib	0.935
2nd line – sunitinib	0.781
3rd line – regorafenib	0.767
Progressed disease	0.647

ERG comment:

- Utility value for PFS in 1st line setting is overestimated - higher than general population utility value of 0.822. ERG preferred utility value is 0.822
- Utility values for 2nd line and 3rd line PFS, and progressed disease appear reasonable.

Issue 7: Utility values in the economic model

Company response from engagement:

- Agree with ERG first-line PFS utility value (0.822)
- Prefer use of VOYAGER utilities for third-line PFS (0.782) and progressed disease (0.727) because these data are:
  - in the relevant patient population
  - more up-to-date than alternatives
  - based on a relatively large sample (n=385)

ERG considerations on company engagement comments:

- Agree VOYAGER data reflect most recent evidence and based on large sample size
- Third-line value from VOYAGER (0.782) higher than second-line (0.781) - considered unrealistic
- Agree VOYAGER utility data appropriate to included in base case, however unable to incorporate change in the time available - Note that inclusion will slightly decrease the ICER.

Technical team: The technical team agree with the adjusted company and ERG base case utility values used in the updated economic model.

KEY QUESTION: Is the company utility value for 3rd line PFS reasonable?

Issue 8: End of life criteria

Short life expectancy: Company modelled mean OS for ECM = **23.72 months**

Extension to life:

- Median OS = not reached in NAVIGATOR study
- Company economic model indicates avapritinib would provide an additional [redacted] life-years

ERG comment: On basis of evidence avapratinib meets requirements to be considered as an end of life therapy.

Technical team: Based on trial evidence and economic modelled data - avapritinib could provide an OS gain of over 3 months. Avapritinib may also meet the short life expectancy criteria.

Company response from engagement:

- Consider avapritinib meets the NICE end-of-life life-extending criteria in this indication
- Median OS in cost-effectiveness model is approximately [redacted] months - likely an overestimate.

ERG considerations on company engagement comments:

- Consider that avapritinib extends life for more than 3 months - company's updated analyses based on the latest data cut for NAVIGATOR do not alter this conclusion.

NCRI-ACP-RCP-RCR:

- Median OS is around 15 months for those with metastatic disease
- OS for those receiving avapritinib is 91% at 12 months and 81% at 24 months (NAVIGATOR).

Technical team (post technical engagement): Avapritinib meets NICE's end of life criteria

KEY QUESTION: Does avapritinib meet NICE's end of life criteria?

Issue 10 (NEW): Treatment dosing pattern in the updated economic model

At technical engagement company submitted a new scenario analysis:

- The relative dose intensity used in the model reflects the 'doseable' days compared to dosed days during NAVIGATOR follow-up for patients still classed as on treatment ([redacted]%). For this updated analysis the company changed [redacted]% to 50% assuming no loss of efficacy.

Company rationale

- UK-based clinical expert indicated some clinicians may use an alternate-day dosing pattern for avapritinib in clinical practice (same concentration every other day)
- Supported by several other international clinical experts at an advisory board - used alternate-day dosing without observing loss of efficacy
- 2 case studies (submitted as supplementary material as academic-in-confidence until publication) - suggests treatment breaks are likely to be more commonly used in clinical practice than in NAVIGATOR to manage toxicity without efficacy loss.

Issue 10 (NEW): Treatment dosing pattern in the updated economic model

ERG comment:

- No specific information from "UK-based clinical expert" provided by company, nor has the reference *GIST Advisory Board 10 February 2020* so cannot validate statement about alternate-day dosing
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

  Could be considered hypothesis generating but should not be taken as evidence that all patients will experience a prolonged post-treatment effect.

Technical team judgement: It is uncertain whether the alternate-day dosing for avapritinib would be considered standard clinical practice in the NHS in England.

KEY QUESTION: Would the alternate-day dosing pattern for avapritinib be standard clinical practice in the NHS in England?

NOTE: Identified post technical engagement

Issue 11 (NEW): Dose reduction and drug wastage

Summary of Product Characteristics for AYVAKYT (avapritinib) states:

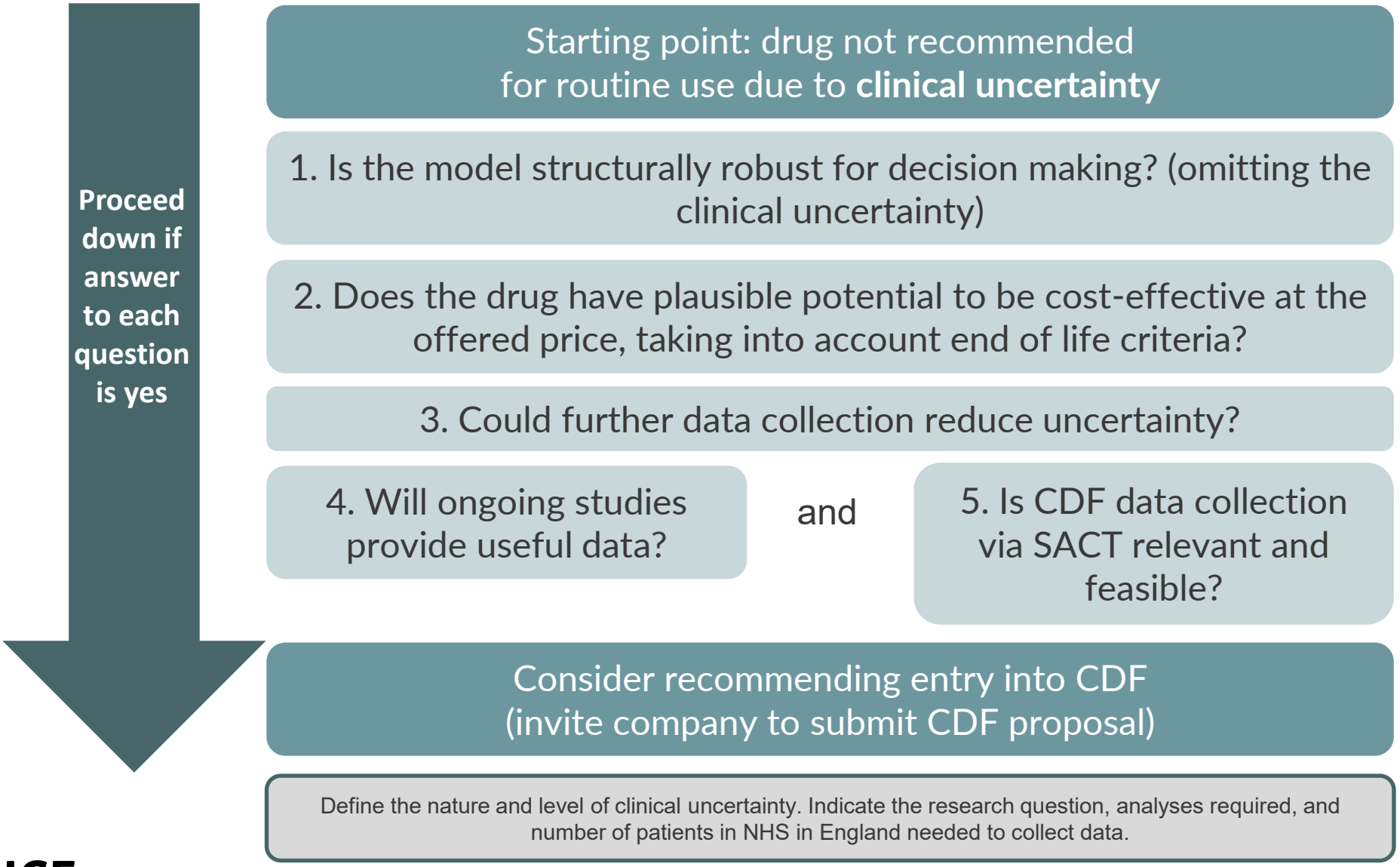
- 'The recommended starting dose of avapritinib is 300 mg orally once daily'
- 'The dose should be adjusted based on safety and tolerability'
- 'In the NAVIGATOR trial, 71% of patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation had dose reductions to 200 mg or 100 mg once daily during the course of therapy'
- 'Median time to dose reduction was 12 weeks'
- 'At 12 months, 27 patients were still on AYVAKYT with 22% receiving 300 mg once daily, 37% receiving 200 mg once daily and 41% receiving 100 mg once daily'

- No analyses to account for drug wastage costs for patients receiving the recommended starting dose who require a dose-reduction

KEY QUESTION: Should dose reduction and drug wastage be included in the cost-effectiveness analysis?

Issue 9: Cancer Drugs Fund

Committee decision making criteria:



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Issue 9: Cancer Drugs Fund

Company submission:

- Acknowledge uncertainty with respect to overall survival and patient HRQoL
- More data from ongoing studies NAVIGATOR and VOYAGER will reduced uncertainty
- Avapritinib should be placed in the Cancer Drugs Fund.

Technical team (pre-consultation):

- Data is immature - further data from NAVIGATOR and VOYAGER may help reduce uncertainty
- At current value proposition, no plausible potential for cost-effectiveness - ICERs all above £20,000–£30,000 per QALY gained range when commercial arrangements considered.

Company response from engagement:

- Kaplan–Meier data are immature - considerable uncertainty surrounding expected and median survival
- Increase in follow-up should allow NAVIGATOR to approach median overall survival, while meeting median progression-free survival and time-on-treatment - will considerably reduce remaining uncertainty
- [redacted]

Issue 9: Cancer Drugs Fund

NCRI-ACP-RCP-RCR:

- Additional data collection would be beneficial.

ERG considerations on company engagement comments:

- Agree entry into the CDF would reduce some uncertainty in cost effectiveness by enabling collection of more mature survival data
- Dosing and dose breaks: may potentially enable investigation of whether patients treated with alternate-day dosing would have the same efficacy as daily dosing, however not clear how much new information may become available and potential risk that uncertainty in the dosing regimen may not be reduced unless there are enough clinical cases with variations on the standard 300mg daily dose.

Technical team (post-consultation):

- Data is immature - further data may help reduce uncertainty
- Updated value proposition: no plausible potential for cost-effectiveness - ICERs above acceptable range when commercial arrangement for avapritinib considered.

KEY QUESTION: Does avapritinib meet the criteria for inclusion in the Cancer Drugs Fund?

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Cost-effectiveness results (1)

NOTE: Results do not include cPAS – will be considered in PART 2

Updated company base-case assumptions with March 2020 data cut	
Time on treatment extrapolation model (issue 3)	Weibull (ERG preferred)
OS extrapolation model (issue 4)	Weibull for both avapritinib and ECM* (ERG preferred)
PFS extrapolation model (issue 5)	Weibull for all lines of treatment (ERG preferred)
Treatment effect duration (issue 6)	18 months
Utility values (issue 7)	PFS 1st line = 0.822 (ERG preferred) PFS 2nd line = 0.781 PFS 3rd line = 0. 782 (Voyager study) Progressed disease = 0.727 (Voyager study)
Alternate-day dosing (issue 10 - NEW)	Same concentration every other day

Company base-case (including commercial arrangement for avapritinib)

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY gained)
ECM*	[redacted]	[redacted]			
avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	£80,342

Company base-case: Alternate-day dosing (including arrangement for avapritinib)

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY gained)
ECM*	[redacted]	[redacted]			
avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	£45,954

*established clinical management

NOTE: Results do not include cPAS – will be considered in PART 2

Cost-effectiveness results (2)

Updated ERG preferred base-case with March 2020 data cut (including commercial arrangement for avapritinib)

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY gained)
ECM*	[redacted]	[redacted]			
avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	£125,309

Updated ERG preferred base-case: Alternate-day dosing with March 2020 data cut (including commercial arrangement for avapritinib)

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY gained)
ECM*	[redacted]	[redacted]			
avapritinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*established clinical management

Key assumptions:

- ECM: proportion of patients receiving 1L (20%); 2L (10%) and 3L (10%) TKIs
- Duration of treatment effect: 1 month

NICE

NOTE: requested by NICE after technical engagement

Cost-effectiveness results (3)

- Extrapolation of the full OS data from NAVIGATOR IPW analysis
- Uncensored for discontinuation
- March 2020 data cut
- Post technical engagement company assumptions (including commercial arrangements for avapritinib)

Extrapolation	ICER	ICER (with alternate-day dosing)
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

Key assumptions:

- ECM: proportion of patients receiving 1L (100%); 2L (100%) and 3L (100%) TKIs
- Weibull distribution applied for ECM overall survival

Note: the company's updated base-case ICER (post technical engagement) = £80,342 per QALY gained and £45,954 per QALY gained with alternate day dosing

CONFIDENTIAL

NOTE: requested by NICE after technical engagement

Cost-effectiveness results – 1st line avapritinib (n=[redacted])

- Extrapolation of the full OS data from NAVIGATOR IPW analysis
- uncensored for discontinuation
- March 2020 data cut
- Post technical engagement company assumptions (including commercial arrangements for avapritinib)

Extrapolation	ICER	ICER (with alternate-day dosing)
Weibull	[redacted]	[redacted]
Exponential	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

Key assumptions:

- ECM: proportion of patients receiving 1L (100%); 2L (100%) and 3L (100%) TKIs
- Duration of treatment waning: 18 months

Note: the company's updated base-case ICER (post technical engagement) = £80,342 per QALY gained and £45,954 per QALY gained with alternate day dosing when receiving avapritinib at all lines of therapy

Key questions

Treatment pathway in economic model: Does the treatment pathway in the economic model reflect that seen in the NHS in England? (Issue 1)

Generalisability of the NAVIGATOR and BLU-285-1002 clinical study populations for prior use of TKIs: Are the populations in the clinical studies generalisable to the NHS in England? (Issue 2)

Extrapolation of overall survival: What is the most appropriate approach to extrapolation of OS? (Issue 4)

Treatment effect duration: What is the most appropriate treatment effect duration? (Issue 6)

Utility values in the economic model: Is the company utility value for 3rd line PFS reasonable? (Issue 7)

End of Life criteria: Does avapritinib meet NICE's end of life criteria? (Issue 8)

Treatment dosing pattern in economic model: Would the alternate-day dosing pattern for avapritinib be standard clinical practice in the NHS in England? (Issue 10: NEW)

Dose reduction and drug wastage: Should dose reduction and drug wastage be included in the cost-effectiveness analysis? (Issue 11: NEW)

Cancer Drugs Fund: Does avapritinib meet the criteria for inclusion in the Cancer Drugs Fund? (Issue 9)