Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more therapies [ID3805]

For public – does not contain confidential information

Technology appraisal committee D [16 February 2023]

Chair: Stephen Smith

Lead team: Carole Pitkeathley, Rebecca Payne, Giles Monnickendam

Evidence assessment group: School of Health and Related Research Sheffield (ScHARR)

Technical team: Emily Leckenby, Caron Jones, Linda Landells

Company: Deciphera Pharmaceuticals

RECAP

Background and treatment pathway

Causes

- Type of soft tissue sarcoma which develops in digestive tract; advanced when spread to other parts of body

Epidemiology

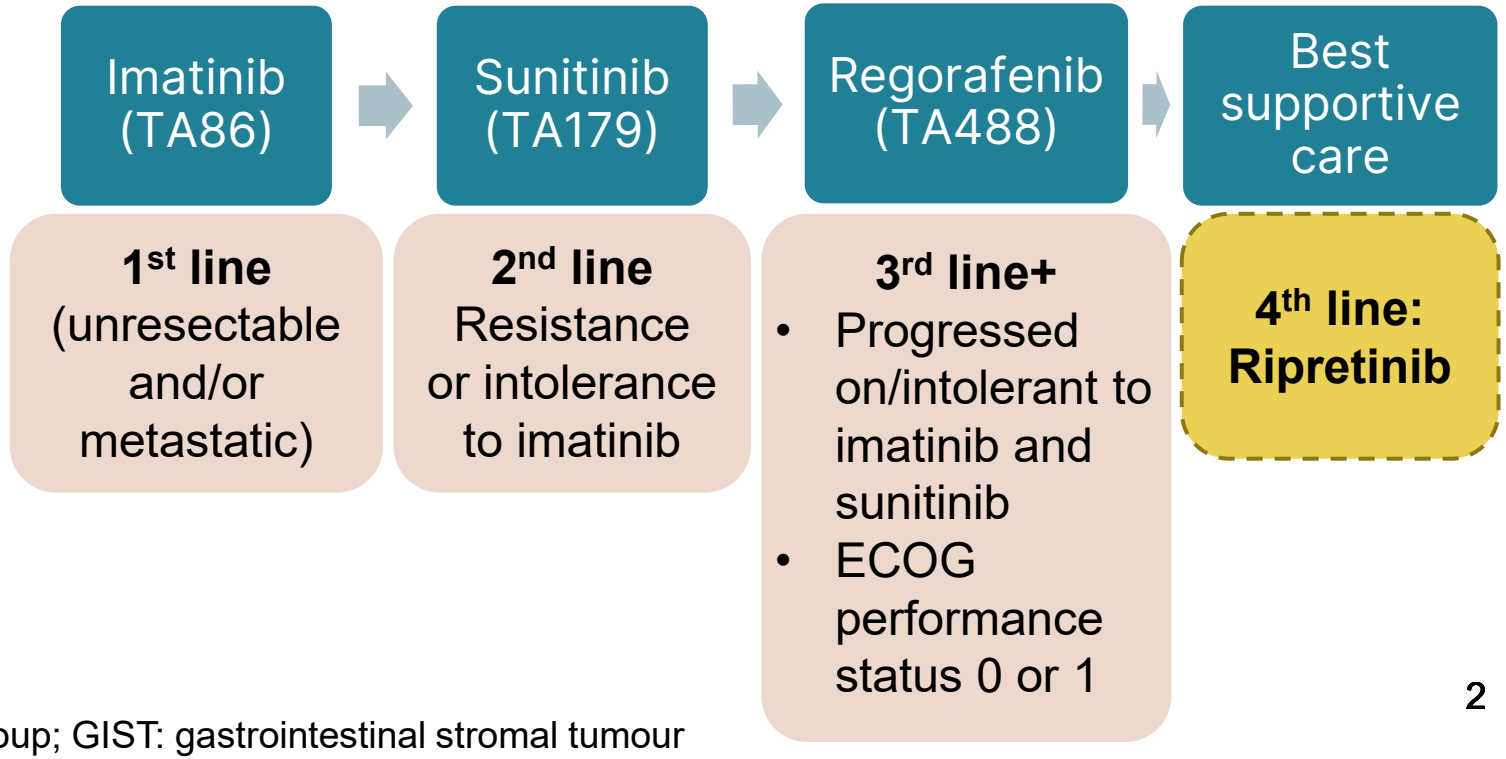
- Approx. 927 new diagnosis/year in UK; median age at diagnosis: 60-65 years, but can occur at any age

Classification

- >85% of cases: activating mutation in tyrosine-protein kinase KIT, CD117 (KIT) or platelet derived growth factor receptor alpha (PDGFRA) gene

Treatment options

- Currently no pharmacological treatment recommended for GIST progressed after 3rd line treatment



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Abbreviations: ECOG: Eastern Cooperative Oncology Group; GIST: gastrointestinal stromal tumour

ACD: preliminary recommendation

Ripretinib is not recommended, within its marketing authorisation, for treating advanced gastrointestinal stromal tumour (GIST) in adults after 3 or more kinase inhibitors, including imatinib

Reason the committee made this decision:

Issues with company's modelling approach and validity of outputs; high level of uncertainty

- 37% of INVICTUS population had 4+ prior treatments; treatment effect modifier (ACD 3.4)
- Model includes stopping rule; does not reflect clinical practice (ACD 3.5)
- Overall survival modelling extrapolations are not clinically valid (ACD 3.6)
- Utility value for ripretinib arm after progression was not plausible (ACD 3.8)

Company's base case ICER not plausible, adjusting overall survival for post-progression ripretinib caused ICER to massively exceed acceptable range (>£100,000)

Consultation responses received from:

- Deciphera Pharmaceuticals (company) – **no new evidence/analysis/price change**
- PAWS-GIST (patient/carer group)

Addressing committee's preferred assumptions (ACD 3.10)

To address the committee's preferred assumptions, several updates to the model were needed:

Requested change	Updated by company?	ERG commentary
Remove the stopping rule because it is not clinically appropriate and disadvantages people with advanced GIST	No	• ERG's previous concerns regarding plausibility of company's survival model predictions (report, TE response) remain unchanged
Ensure the outputs of the model are clinically validated and align with clinical opinion on survival estimates	No	
Adjust overall survival and progression-free survival estimates to account for dose escalation and treatment switching in the INVICTUS trial	No	
Include scenario analyses for both the company's and ERG's preferred utility values	No	• Concerns with utility value in model • Company does not provide alternative health utility values for PD state
Include the ERG's preferred drug wastage of 0.25 of a pack per person	No	• Retains view that some level of wastage should be included in model

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Abbreviations: OS: overall survival; PD: progressed disease; TE: technical engagement

Summary of company ACD response and ERG critique (1)

ACD section	Company comments	ERG comments
3.6/3.7 – OS extrapolation/ economic modelling	• Reimbursement sought up to progression only • UK clinicians advised treatment would be stopped at clear progression • Level of evidence insufficient to assume additional survival benefit post-progression	• **Concerns about plausibility of company's survival model predictions unchanged** • Assumption that post-progression ripretinib use not influenced OS inappropriate • ERG clinical advisers: post-progression ripretinib influenced OS in INVICTUS

3.6 –analyses exploring OS after disease progression	• Further extrapolation methods explored in model – option to adjust OS for those in ripretinib arm continuing ripretinib after disease progression using multiple methods:
	  • Simple two-stage adjusted with/without re-censoring, complex two-stage with/without re-censoring, rank preserving failure time model with/without re-censoring
		• ERG misunderstood drop down menu within model provided at TE; has been able to explore impact of each alternative switching methods on ICER
		  • Additional analysis may not be relevant for decision making as includes stopping rule
		• **Most appropriate analysis**: adjusting OS to account for treatment switching in BSC group only, and estimating ripretinib treatment costs using parametric survival models fitted to TTD data
		  • **TTD data not been presented** by company at any point during this appraisal

Abbreviations: BSC: best supportive care; OS: overall survival; TE: technical engagement; TTD: time to discontinuation

Summary of company ACD response and ERG critique (2)

ACD section	Company comments	ERG comments
3.8 – side effects associated with regorafenib	• Post-progression utility value from GRID trial independent of treatment; was observed in some patients receiving open-label regorafenib • Side effects that led to low value of 0.647 may be due to regorafenib still be administered, not persisting outside its therapeutic window	• Agree that low utility values reported by GRID potentially subject to confounding • **ERG has concerns with utility value in model ([redacted])**; small sample size, minor impact of HRQoL, doesn't reflect mean utility over entire remaining survival time • ERG's TE response: utility value for PD state **doesn't substantially impact ICER**
3.9 – drug wastage	• UK clinicians stated patients closely monitored (every 28 days) • Prescription/supply closely matched to patients' level of progression • Wastage tightly controlled; would affect <5% of patients	• Some level of wastage incurred by any patient taking oral therapy if they stop for any reason (intolerance, progression, death) • **Wastage should be included in model**

ERG summary: **preferred analysis remains unchanged from ERG report/ACM1**

Abbreviations: HRQoL: health related quality of life; PD: progressed disease; TE: technical engagement

Summary of PAWS-GIST response

Theme	PAWS-GIST comments
Relevant evidence	• Evidence in favour of ripretinib as fourth line treatment in GIST is robust

Interpretation of evidence	• Biased towards ripretinib being stopped purely based on radiological evidence, rather than combination of clinical and radiological evidence
	  • Standard used internationally when identifying progression disease in GIST
	• In GIST, possible to mistakenly interpret radiological changes as progression when in fact response to treatment:
	  • Potential misinterpretation of the images produced by complex tumour response patterns to TKIs can lead to false diagnosis of progression
	  • Response assessment is complex; early progression in particular should be confirmed by team experienced in treating GIST
	  • Tumour size may increase in short term, but if tumour density on CT scan is decreased, this may indicate tumour response
	• **Clinicians will continue to use drug where there is benefit to patient; when treatment clearly stops working, standard practice to stop using treatment**

PAWS-GIST summary: **supports the committee's position on stopping rule**

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Abbreviations: GIST: gastrointestinal stromal tumour

Cost-effectiveness results

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

NICE National Institute for Health and Care Excellence

Thank you