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

For public – contains no confidential information

Technology appraisal committee D [2 November 2022]

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Company: Deciphera Pharmaceuticals

Background on gastrointestinal stromal tumours (GIST)

Causes

- Gastrointestinal stromal tumours (GIST) are a type of soft tissue sarcoma (cancer) which develops in the digestive tract
- In advanced GIST the tumours will have started to spread to other parts of the body e.g., liver or peritoneum

Epidemiology

- Approximately 927 new diagnoses per year in the UK (CancerData)
- Median age at diagnosis: 60 to 65 years, but GIST can occur at any age

Classification

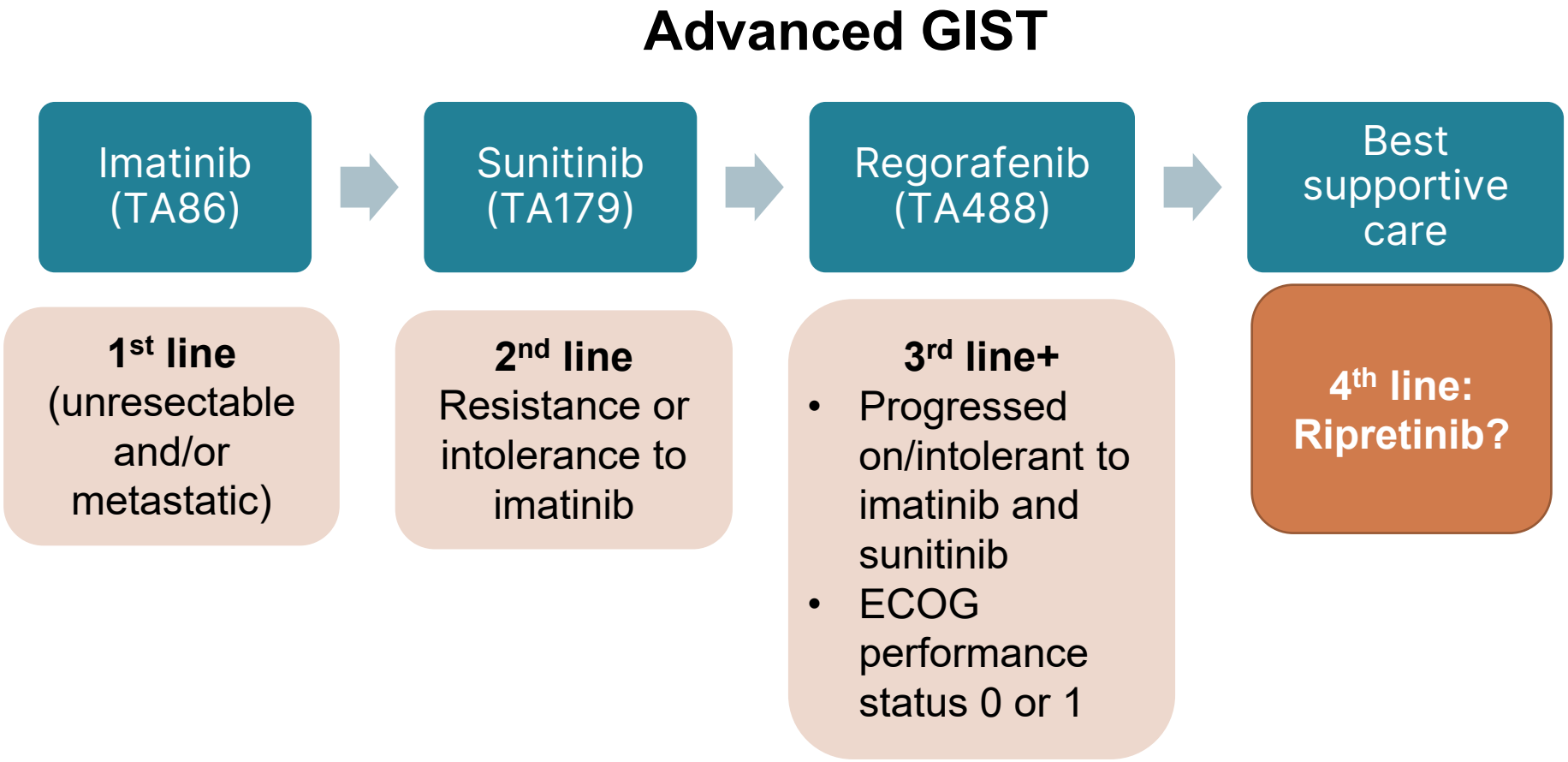
- In over 85% of advanced GIST the activating mutation in tyrosine-protein kinase KIT, CD117 (KIT) or platelet derived growth factor receptor alpha (PDGFRA) gene is found

Treatment options

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

Treatment pathway

Ripretinib is positioned in 4th line advanced GIST



NICE

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

Patient perspectives

Submissions: Andrea Weston; Katy Jones-Cole; GIST Cancer UK; Sarcoma UK

Unmet need for people who cannot have surgery or current treatments

Ineffective current treatments – primary and secondary KIT and PDGRA mutations in GIST mean current treatments are not effective

- Ripretinib inhibits a range of KIT and PDGFRA mutations, so offers a further option for people, which can prolong survival

Carers – people with GIST can live 'normal' lives while managing side effects, but can have problems looking after themselves

Side-effects of current treatments include: fatigue, diarrhoea, hypertension, hyperthyroidism, nausea or vomiting

- Diagnosis affects mental health and wellbeing in 95% of people
- Ripretinib is administered orally and is well tolerated

Ripretinib side-effects include: alopecia, hand-foot syndrome, 'severe' muscle cramps, diarrhoea, cardiac problems

"Ripretinib gives hope to patients who have exhausted current treatment options"

"Side effects are much milder [than sunitinib and regorafenib]. I lead a normal life…work, travel, exercise without too much restriction"

"I want to lead my life alongside my condition…not just be a cancer patient"

"The traumas and horrors of living with a type of GIST cancer that does not have a treatment that works can shatter family's lives"

"GIST patients in the UK deserve access to ripretinib as people in the rest of the world"

"Ripretinib has allowed me to continue with a good quality of life, as I have adapted to cope with the side effects"

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Abbreviations: GIST: gastrointestinal stromal tumour; PDGFRA: platelet derived growth factor receptor alpha

Clinical perspectives

Submissions: Dr Ramesh Bulusu and Dr Charlotte Benson

Unmet need – there is no treatment option in 4th line setting except symptomatic management or best supportive care

- Ripretinib would be an important option for all GIST in 4th line setting (taking into account performance status and organ function)

Advance in treatment – ripretinib offers important progress in managing advanced GIST as the first new treatment in over 5 years

Expect symptom benefit – improved progression-free survival, improved overall survival, and manageable side effects

- Clinicians are familiar with common side effects with ripretinib (include fatigue, diarrhoea, hypertension, palmar plantar erythema) – common to other TKIs in GIST

No further resources required for management – oral treatment and established network of GIST clinics

"There is desperate unmet need for a 4th line therapy in metastatic/inoperable GIST patients and ripretinib fulfils that unmet need"

"This is a significant 'step change' the first in 5 years since the licensing of regorafenib"

"In my own UK practice…I have looked after a number of patients on expanded access ripretinib in the 4th line setting who have had clinical benefit from the treatment and toxicity is manageable…"

Abbreviations: GIST: gastrointestinal stromal tumour; TKI: tyrosine kinase inhibitor

Other considerations

Equality considerations

- No equality considerations to consider

Innovation

Company describe ripretinib as innovative because:

- It can broadly inhibit wild-type and mutated KIT and PDGFRA and addresses an unmet need
- It shows clinical efficacy and an ‘acceptable safety profile’ from the INVICTUS trial

Clinical experts:

- Ripretinib is a significant ‘step change’ in first 5 years since regorafenib licensing

Abbreviations: PDGFRA: platelet-derived growth factor receptor alpha

Key issues

Issue	ICER impact
• Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	Unknown
• Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	Unknown
• Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	Large
• Proposed stopping rule is not in line with existing recommendations on the use of tyrosine kinase inhibitors	Unknown
• Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy	Moderate

Additional issues	ICER impact
• Exclusion of drug wastage costs	Small

Ripretinib (QINLOCK, Deciphera)

Marketing authorisation	'For the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib' • MHRA December 2021
Mechanism of action	• Ripretinib works to slow tumour cell growth by blocking the activity of KIT and PDGFRA receptor tyrosine kinases on the surface of cancer cells • It can also inhibit other kinases *in vitro*
Administration	• 150 mg (3 x 50 mg) tablets, once a day • Continue as long as benefit is observed or until unacceptable toxicity
Price	• List price: £18,400 for 30 day supply • Patient Access Scheme has been approved

Abbreviations: GIST: gastrointestinal stromal tumour; MHRA: medicines and healthcare products regulatory agency; PDGFRA: platelet derived growth factor receptor alpha

Decision problem

In line with NICE scope but potential issues with population, intervention and comparators

	Final scope	Company	ERG comments
Population	Adults with advanced GIST who have had at least 3 prior therapies, or have documented intolerance to any of these treatments	Specify prior treatment with 3 or more kinase inhibitors, including imatinib as per marketing authorisation	Company have ripretinib as 4th line therapy; some people in INVICTUS trial had 3 to 7 prior treatments at baseline
Intervention	Ripretinib		Company seek recommendation until progression but ripretinib allowed to continue after progression in trial and MA
Comparators	Established clinical management without ripretinib including best supportive care (BSC)		Some people have regorafenib beyond progression rather than BSC in usual practice
Outcomes	OS; PFS; response rate (including partial response rate and duration of response); adverse events; health-related quality of life (HRQoL)		Model uses data from INVICTUS on OS, PFS, AEs and HRQOL

Abbreviations: AE: adverse event; GIST: gastrointestinal stromal tumour; MA: marketing authorisation; OS: overall survival; PFS: progression-free survival

Clinical effectiveness

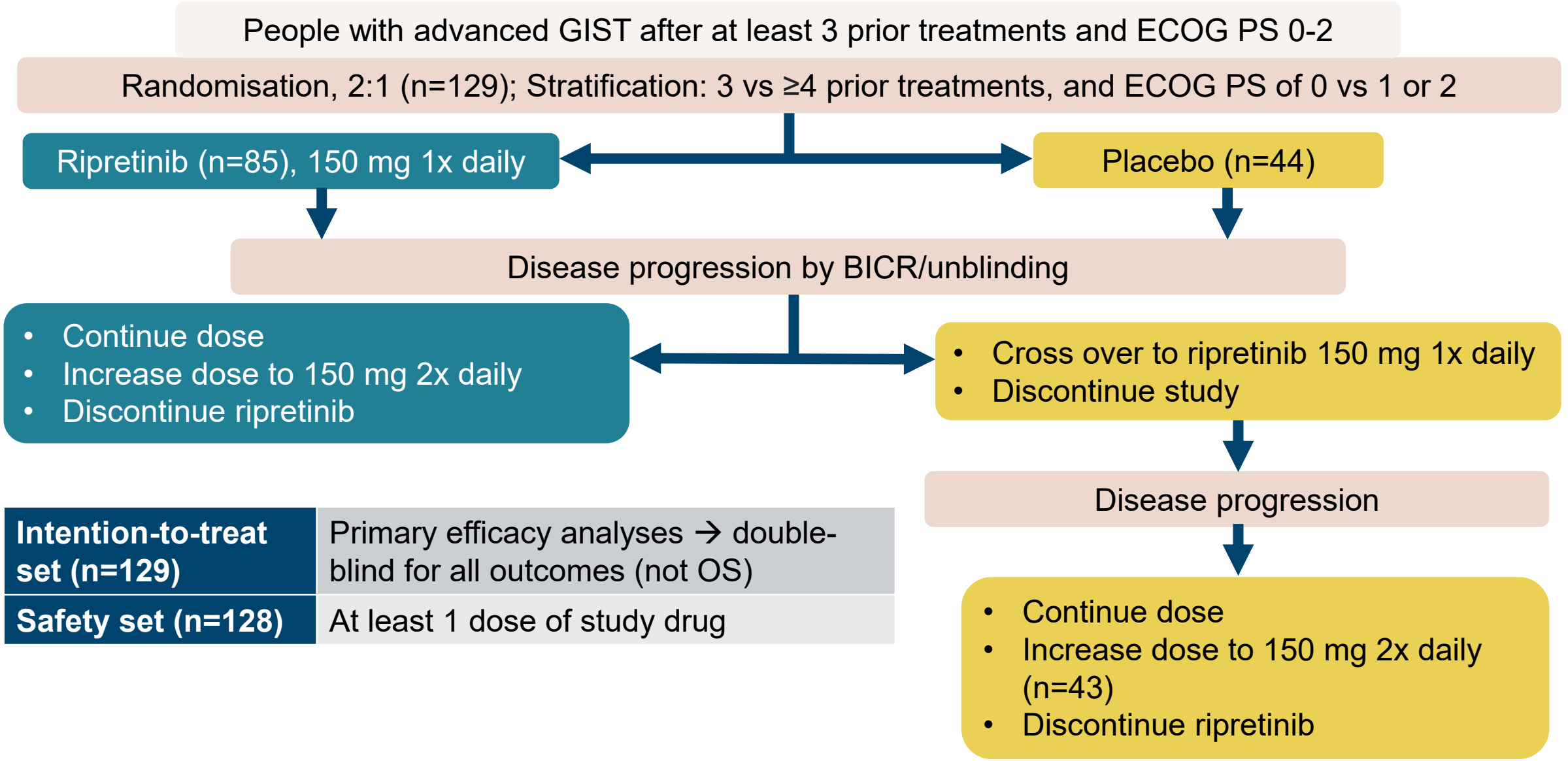
NICE National Institute for Health and Care Excellence

Key clinical trial: INVICTUS

INVICTUS trial characteristics	
Design	Phase 3 double-blind, placebo-controlled, randomised trial
Population	People with advanced GIST after at least 3 prior treatments (imatinib, sunitinib, regorafenib), and ECOG performance score 0-2
Intervention	Ripretinib plus best supportive care until disease progression (can discontinue or continue with current or double dose), or unacceptable toxicity
Comparator	Placebo plus best supportive care – can discontinue or switch to ripretinib on disease progression
Duration	Primary data-cut: May 2019 (median 6.3 months follow-up) → additional follow-ups after 9 months and 19 months
Primary outcome	Progression-free survival assessed by blinded independent central review
Secondary outcomes	Objective response rate (key secondary outcome); overall survival; time to progression; duration of response; health-related quality of life
Locations	International, multicentre (North America, Europe, Asia) 10 out of 129 people from 2 UK sites

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

INVICTUS study design (1)



Intention-to-treat set (n=129)	Primary efficacy analyses → double-blind for all outcomes (not OS)
Safety set (n=128)	At least 1 dose of study drug

Abbreviations: BICR: blinded independent central review; OS: overall survival

INVICTUS study design (2)

Treatment switching: placebo arm could discontinue or switch to ripretinib 1x day on progression

- Study was unblinded on progression
- **ERG:** May have an impact on overall survival – measured until death

Status	Ripretinib	Placebo
Randomised	85	44
Moved to open-label ripretinib (1x or 2x dose)	42 (49%)	29 (66%)
Total still having ripretinib	36 (42%)	11 (25%)
Total discontinued or not having ripretinib	49 (58%)	33 (75%)

Dose escalation: People in ripretinib arm could discontinue, continue 150mg daily dose, or increase to 150 mg 2x day

- Company rationale: higher dose well tolerated in a Phase 1 study and lack of alternatives
- SPC: 150 mg 1x day is recommended dose

Median duration of ripretinib 150 mg 2x day treatment: 3.7 months (range 1 day to 18.6 months); 26% (11/43) had 2x dose for ≥6 months

- Company did not provide number of people having ripretinib 1x day post-progression and duration

INVICTUS overall and progression-free survival results

Increase in median overall and progression-free survival for people having ripretinib compared with placebo

	January 2021 cut-off (ITT)	
	Ripretinib (n=85)	Placebo (n=44)
Overall survival		
Median, months (95% CI)	18.2	6.3
Hazard ratio (95% CI)	0.41 (0.26 to 0.65)	
Progression-free survival		
Median, months (95% CI)	6.3	1.0
Hazard ratio (95% CI)	0.16 (0.10 to 0.27)	
P-value	P<0.0001	

Primary outcome cut-off: May 2019

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Abbreviations: CI: confidence interval; ITT: intention-to-treat

INVICTUS overall and progression-free survival crossover results

Improvement in median overall and progression-free survival for people crossing over from placebo to ripretinib

		January 2021 cut-off (ITT)
Overall survival		
Crossover (placebo to ripretinib, n=30)	Median, months (95% CI)	10.0
No crossover (placebo, n=[redacted])	Median, months (95% CI)	[redacted]
Progression-free survival		
Crossover (placebo to ripretinib, n=29)*	Median, months (95% CI)	4.6 (1.8 to Not Estimable)
Event, n (%)		13 (45)
Patients censored, n (%)		16 (55)

***Exploratory analysis in open-label phase (cut-off not reported)**

Abbreviations: CI: confidence interval; ITT: intention-to-treat

Key issue: INVICTUS population differs with target population

Different numbers of prior treatments in INVICTUS and clinical practice may be prognostic factor or treatment effect modifier

Background: Company intend ripretinib as 4th line treatment but 37% in INVICTUS have ≥4 treatments → mismatch with intended positioning of ripretinib and clinical evidence, as model is informed by ITT

Company: Ripretinib efficacy in 4th line is conservative using full INVICTUS population in model

- UK advisory board (Aug 22) expect same/better outcomes for 4th line ripretinib than in INVICTUS

ERG: Unclear if outcomes for ≥4 prior treatments in INVICTUS seen in 4th line in practice

- Concern if a potential treatment effect modifier or prognostic factor
- Can restrict to 3 treatments in model but ↓sample and may cause confounding (not stratified)
- Company KM plot for OS by subgroup (3 and ≥4 prior treatment) exclude adjustments for post-progression ripretinib → difficult to interpret (potential confounding)
- PFS (unaffected by open-label ripretinib) KM plots do not indicate better or worse result for 3 vs ≥4 treatments → limited conclusions: small subgroups (mainly in placebo) and data subject to high censoring at later timepoints

Clinical experts: People in trials usually fitter but in UK, most have 3 prior treatments so may respond better and have less resistance mutations; ECOG 1 or 2 in INVICTUS suitable for 4th line ripretinib

Is the number of prior treatments likely a treatment effect modifier or prognostic factor?

Abbreviations: ECOG: Eastern Cooperative Oncology Group; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor

Subgroup analysis

Overall survival for 3 prior treatments is more favourable than 4 or more

Pre-specified subgroup		Ripretinib vs placebo hazard ratio (95% CI)	
		PFS (May 2019)	OS (January 2021)
Age (years)	18 to 64	0.25 (0.14 to 0.45)	0.42 (0.23 to 0.75)
	64 to 74	0.18 (0.06 to 0.56)	0.46 (0.19 to 1.08)
	≥75	0.03 (0.00 to 0.56)	0.41 (0.13 to 1.31)
Number of prior treatments	3 (n=54 ripretinib)	0.15 (0.08 to 0.29)	0.31 (0.18 to 0.54)
	≥4 (n=31 ripretinib)	0.24 (0.12 to 0.51)	0.63 (0.31 to 1.29)

Other pre-specified subgroups: Gender, Race, Region, ECOG performance score

ERG: Company informed that data on PFS and OS sub-grouped according to progression, resistance, or intolerance to prior TKIs (as suggested in NICE scope) were not recorded

- PFS generally consistent across subgroups but some had small number of people → difficult to interpret
- OS comparable across age groups; [redacted]

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Abbreviations: ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor

Key issue: Post-progression regorafenib as a comparator

Company and ERG have different views; limited evidence for a comparison

Company: BSC is only appropriate comparator for 4th-line ripretinib aligned with TA179, TA488

- Clinical advice: Ripretinib availability would not affect stopping decision for regorafenib
- Indirect treatment comparison unlikely possible because of small numbers of people with ≥4th line regorafenib in clinical trials found (Kang 2021 and Serrano 2019)

ERG: Regorafenib post-progression is relevant comparator; clinicians would switch to ripretinib

- Agree BSC was only comparator for TA179 and TA488 but both indicate continuation possible after disease progression in clinical practice
- Clinical advice: 50% or more people continue regorafenib post-progression if there is still clinical benefit, no significant toxicity or rapid disease progression, and no further treatments available
    - If recommended, would switch people to 4th line ripretinib if progressed with 3rd line regorafenib

Clinical experts: Unlikely for future RCTs comparing ripretinib with post-progression regorafenib

- If ripretinib is available, will likely switch from regorafenib to ripretinib after progression

Patient experts: Post-progression regorafenib used because last line of treatment to maximise treatment benefit – comparison should be with BSC

Is post-progression regorafenib an appropriate comparison to include?

Abbreviations: BSC: best supportive care; GIST: gastrointestinal stromal tumour; RCT: randomised controlled trial

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model: Key parameters

Evidence used in company's base case analysis	
Population	Advanced GIST after 3 treatments including imatinib
Baseline characteristics	60.1 years of age; 43.4% assumed female
Intervention	Ripretinib 150 mg once daily (plus best supportive care)
Comparator	Best supportive care
Clinical efficacy and safety	INVICTUS (primary source); published clinical evidence; UK population general mortality
Treatment duration	Ripretinib discontinued at disease progression – no further active treatment (assume TTD = PFS)
Cycle length	Monthly (28 days) with half-cycle correction
Time horizon	40 years (lifetime)
Utilities	EQ-5D-5L (INVICTUS) mapped onto EQ-5D-3L
Adverse event disutilities	Harrow et al. (2011), Doyle et al. (2008), and assumptions
Costs	Drug acquisition, health state management, pre-treatment resource use, palliative treatments, management of adverse events, end of life

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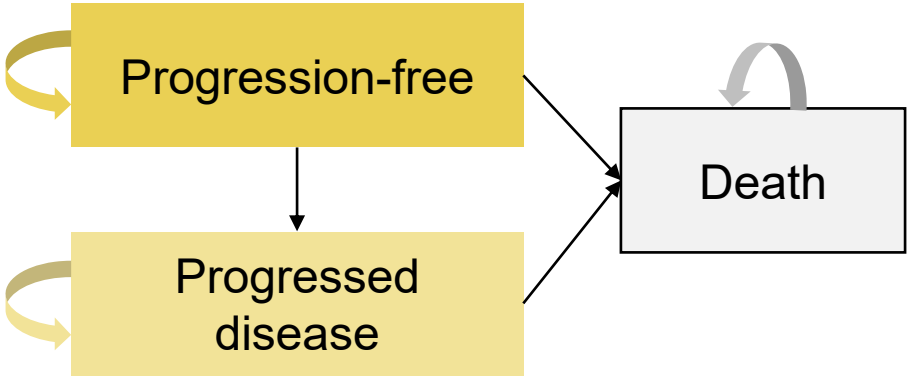
Abbreviations: EQ-5D-5L: EuroQol 5 Dimension; GIST: gastrointestinal stromal tumour; PFS: progression-free survival; TTD: time-to-treatment discontinuation

Company's model overview

Model structure:

- Partitioned survival model; 3 health states
- Informed by TA86, TA179, TA488



- **TA86:** imatinib for unresectable or metastatic GIST
- **TA179:** sunitinib for GIST
- **TA488:** regorafenib for previously treated unresectable/metastatic GIST

Ripretinib affects costs by:

- ↑ overall costs → acquisition cost of ripretinib
- ↑ overall disease management costs → extended overall survival
- ↑ costs associated with managing adverse events

Ripretinib affects QALYs by:

- ↑ progression-free survival
- ↑ overall survival
- ↓ (slightly)HRQoL → higher burden of adverse events

Assumptions with greatest ICER effect:

- Ripretinib treatment duration – application of stopping rule
- Adjustment to ripretinib OS, to align with stopping rule
- Parametric survival model fitted to OS data
- Utility value applied for progressed disease health state

Abbreviations: GIST: gastrointestinal stromal tumour; ICER: incremental cost-effectiveness ratio; HRQoL: health-related quality of life; OS: overall survival; QALY: quality-adjusted life year

Key issues: Company vs ERG assumptions

Key input	Company	ERG
Ripretinib treatment duration	**TTD assumed equal to PFS** • Seeking positive NICE recommendation for ripretinib up to disease progression only • Company's clinical experts advised that ripretinib treatment would be stopped at clear progression.	**TTD equal to PFS, although ERG recommends analysis with continued use** • Treatment beyond progression in INVICTUS • Company proposed stopping rule conflicts with TKI guidance in GIST • INVICTUS TTD data not made available to model continued use → ERG models TTD equal to PFS (while adjusting OS)
Adjustment for ripretinib treatment beyond progression	**No adjustment to ripretinib OS for continued treatment beyond progression** • Disagree ripretinib may result in additional survival benefit when used post progression • Limited data to implement adjustment • Uncertainty in appropriate method and size/direction of potential bias	**Adjust for post-progression ripretinib using simple two-stage method with re-censoring** • 49% ripretinib patients in INVICTUS continued to open-label ripretinib after progression • Clinical advice supports and company analysis indicates OS benefit from continuation • Adjusting OS is consistent with proposed stopping rule
Survival model	**Log-normal for PFS and OS for both treatment arms** • Independent models fitted to PFS and OS • Log-normal selected for all extrapolations, based on visual and statistical goodness of fit (lowest AIC/BIC)	**Log-normal for PFS, generalised gamma for OS** • Company predictions for ripretinib OS not clinically plausible • Company model selection does not consider empirical hazard, modelled hazard function and clinical plausibility • After adjusting OS data for post-progression ripretinib, generalised gamma considered most plausible for ripretinib OS
Post-progression utilities	**Post progression utility value of [redacted], from INVICTUS** • Updated analysis provided, excluding HRQoL from people continuing ripretinib after progression • Utility value from regorafenib in GRID trial not appropriate, due to differences in tolerability	**Post progression utility value of 0.647, sourced from GRID trial** • Company value for progressed disease is high, compared with pre-progression value and values from other trials in earlier lines • Company analysis is based on a small sub-set of HRQoL surveys, with potential selection bias and informative censoring

Abbreviations: GIST: gastrointestinal stromal tumour; HRQoL: health-related quality of life; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor; TTD: time-to-treatment discontinuation

Key issue: Ripretinib treatment duration

Stopping ripretinib at disease-progression may not align with clinical practice

Background: Company model applies stopping rule for ripretinib at disease progression

Company: Seeking positive NICE recommendation for ripretinib up to disease progression only

- Clinical advisory board: Treatment would stop at clear progression
- Exceptions may be for heavily pre-treated GIST if radiological progression is limited and treatment is tolerated – but for minority of people and only if no other treatment options

ERG: Company's stopping rule conflicts with TKI guidance in GIST

- NCCN & UK GIST guidelines support continuing TKI post progression when no further options available
- 49% INVICTUS ripretinib patients continued to open-label ripretinib after progression
- Clinicians:~50% continue regorafenib (current last line of therapy) post-progression
- Analysis without stopping rule could remove need for ripretinib OS adjustment and allow treatment costs to be based on INVICTUS TTD data

Clinical experts:

- TKIs in kinase-driven cancers usually continue until deterioration and no further ongoing clinical benefit
- Disease progression is nuanced (radiological response difficult to determine) assessment of ongoing clinical benefit used with radiological response. Stable disease also important

Patient expert: Usually continue TKIs with benefit or else progress faster; progression is nuanced

Does the stopping rule align with clinical practice? Should it be included in the model?

Abbreviations: BSC: best supportive care; GIST: gastrointestinal stromal tumour; NCCN: National Comprehensive Cancer Network; OS: overall survival; TKI: tyrosine kinase inhibitor; TTD: time-to-treatment discontinuation

Key issue: Ripretinib use post-progression and overall survival

Overall survival data from INVICTUS not consistent with company's proposed use of ripretinib in clinical practice

Background: In INVICTUS people having BSC could switch to ripretinib after progression

- **People having ripretinib could continue or have higher dose after progression**

Company: Adjusts OS for crossover in BSC arm; no adjustment to ripretinib for post-progression use

- Assume no impact on OS from post-progression ripretinib use – limited data to support
- Uncertainty in appropriate method, size/direction of potential bias
- Simple two-stage estimation with re-censoring and complex model explored in scenario analyses

ERG: Adjust for crossover & post-progression ripretinib with simple 2-stage method with re-censoring

- Post-progression ripretinib expected to improve OS (clinical advice); company's results suggest this
- Company suggest similar trial post-progression and progression-free utility attributed to continued quality of life benefit from ripretinib post-progression
- May be informative to explore other clinically plausible scenarios using simple and complex models, with and without re-censoring (not presented by company)
- Uncertainty on OS benefit size, but average [redacted] year survival having BSC after ripretinib not plausible

Clinical expert: Post-progression ripretinib may slow disease progression in trial but uncertain if influenced OS

Ripretinib	Company	ERG
Mean PFS, yrs	[redacted]	[redacted]
Mean OS, yrs	[redacted]	[redacted]

Should OS be adjusted for post-progression ripretinib use in both arms?

Abbreviations: BSC: best supportive care; OS: overall survival; PFS: progression-free survival; yrs: years

Key issue: Survival modelling for overall survival (1)

Uncertainties in the company's survival modelling identified by the ERG

Background:

- **Company uses unadjusted OS data for ripretinib and fits independent log-normal models – based on low AIC/BIC**
- **ERG uses adjusted OS data for ripretinib and fits generalised gamma models – there is poor fit for OS in ripretinib using standard parametric models**

ERG considers company modelled OS limited, because:

- Company did not consider empirical hazard, modelled hazard function, and clinical plausibility – only goodness-of-fit
- An implicit assumption of lifetime treatment effect on OS despite stopping rule
- Extrapolation of OS in ripretinib group is implausibly optimistic

ERG clinical advisers suggests company OS model lacks clinical plausibility

- Continuing ripretinib beyond disease progression leads to additional OS benefits
- In INVICTUS, almost everyone progressed by 2 years, expect 10-20% alive at 3 years
- Log-normal for may be optimistic for ripretinib after ~1.5 years

ERG preferred model: 2-stage adjusted generalised gamma for both arms

- All models may overestimate OS after around 1 year
- Weibull and exponential give lower mean OS estimates but also likely optimistic; or more plausible when ripretinib continued after progression

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Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BSC: best supportive care; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor

Key issue: Survival modelling for overall survival (2)

Company and ERG's preferred overall survival models for ripretinib

ERG's and company's preferred OS models for ripretinib group

Which extrapolation does the committee prefer to model overall survival?

Abbreviations: BSC: best supportive care; KM: Kaplan-Meier; OS: overall survival; PFS: progression-free survival;

Key issue: Health-related quality of life after 4th line progression

Concern that the utility for progressed disease does not have face validity

Background:

- **Company use [redacted] for progressed disease (post TE, excluding switching to ripretinib)**
- **ERG prefer 0.647 from GRID trial in TA488 (regorafenib) for progressed disease**

Company:

Clinicians did not consider regorafenib from GRID comparable to ripretinib because different tolerability

ERG: Company's utility for progressed disease is high and may lack face validity

- Final EQ-5D assessment in INVICTUS was [redacted]
- Company's post-TE analysis based on people in BSC arm not crossing over to ripretinib after progression → represents small sample ([redacted] in updated vs [redacted] in original analysis) with potential selection bias and informative censoring
- Utility estimates from trials at earlier lines have lower utility in progressed state (except Zolic et al., 2015)

Clinical experts: TKI withdrawal often results in rapid symptomatic deterioration and death

Patient experts: Feedback is that ripretinib tolerated better than regorafenib

Are the utility estimates for progression-free and progressed disease states plausible?

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Abbreviations: AE: adverse event; BSC: best supportive care; EQ-5D: EuroQol 5 Dimension; HRQoL: health-related quality of life; TE: technical engagement; TKI: tyrosine kinase inhibitor

Additional issue: Drug wastage costs excluded

Drug wastage considered captured by company, but ERG prefer including it in model

Background:

- **Company did not include wastage costs – assume packs can be split and any tablets not taken are captured in relative dose intensity**
- **ERG assume 0.25 pack wasted per person on average**

Company: Adding wastage is not appropriate – any wastage would affect <5% people (advisory board)

- Clinicians advised there would be wastage but it would be controlled
- There will be close monitoring every 28 days in this heavily pre-treated setting→ so prescription and supply would closely match progression level

ERG: Some wastage should be included in model – but not key driver of ICER

- Company acknowledge wastage but did not include within its base case
- Wastage is expected when having oral therapy if stopped for any reason before completing a pack – e.g. due to intolerance, progression, death

What level of wastage is appropriate to include in the model?

Abbreviations: ICER: incremental cost-effectiveness ratio

Cost-effectiveness results

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

Summary of company and ERG base case assumptions

Assumption	Company	ERG	ICER impact from different assumptions
Overall survival	Unadjusted in ripretinib group, log-normal	Adjusted in ripretinib group, generalised gamma	Increase by >£50,000
Utility	[redacted] including age-adjustment	0.647 including age-adjustment (GRID trial accepted in TA488 regorafenib)	Increase by <£5,000
Wastage	None	0.25 pack	Increase by <£5,000

Summary:

- The ERGs ICERs are all above the level normally considered an effective use of NHS resources with or without end of life
- The company's base case is below the level normally considered an effective use of NHS resources when considering end of life

Abbreviations: Inc. Incremental; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Scenario analyses to present in Part 2 slides

ICERS reported in Part 2 slides are because of confidential comparator prices

Parameter	**Company base case** • Correction of model errors • Unadjusted overall survival in ripretinib group and log-normal model • Utility for progressed disease based on INVICTUS plus age-adjusted • No drug wastage
	Sensitivity analysis
Progression-free survival	Log-logistic; generalised gamma
Overall survival	Log-logistic; Gompertz
Crossover methods	• Complex 2-stage method with/without re-censoring • Simple 2-stage method without re-censoring • RPSFTM with/without re-censoring
Ripretinib continued use	• Adjustment using simple 2-stage method with re-censoring
Utility	• From TA488 (progression-free: 0.767; progressed disease: 0.647)

Differences between ERG and company base case

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Abbreviations: RPSFTM: rank preserving structural failure time model

Sensitivity analyses to present in Part 2 slides

ICERS reported in Part 2 slides are because of confidential comparator prices

Parameter	ERG base case • Correction of model errors • Include overall survival adjustment in ripretinib group and use generalised gamma model • Utility for progressed disease based on GRID trial plus age-adjusted utility • Include drug wastage (0.25 pack)
	Sensitivity analyses
Progression-free survival	Exponential; Weibull; Gompertz; log-logistic; generalised gamma
Overall survival	Exponential; Weibull; Gompertz; log-normal; log-logistic
Utility	Company updated utility for progressed disease state [redacted]
Wastage	0.5 pack

Differences between ERG and company base case

End-of-life

1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months
2. Sufficient evidence to indicate the treatment has the prospect of offering an extension to life, normally a mean value of at least added 3 months, compared with current NHS treatment

Committee should be satisfied that:

- Estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival
- Assumptions used in the reference case economic modelling are plausible, objective and robust

	Placebo	Ripretinib
Median overall survival	6.6 months	Increase by 8.5 months
Overall survival adjusted for treatment switching	[redacted] months	Increase [redacted] months

		Company	ERG
Mean undiscounted life-years	Best supportive care	[redacted]	[redacted]
	Ripretinib	[redacted]	[redacted]
Incremental life years		[redacted]	[redacted]

Company and ERG agree ripretinib very likely to meet end-of-life criteria

Are end-of-life criteria considered to be met?

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Thank you.