Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments [ID6496] Review of TA881

For screen
contains redacted information

Technology appraisal committee D [15 October 2025]

Chair: Dr Raju Reddy

Lead team: Philip Mallender, Guy Makin, Paul Caulfield

External assessment group: Sheffield Centre for Health and Related Research (SCHARR), University of Sheffield

Technical team: Vicky Gillis-Elliott; Joanna Richardson; Elizabeth Bell

Company: Deciphera

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments

- ✓ **Recommendation and conclusions from TA881**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Ripretinib (Qinlock, Deciphera)

Marketing authorisation	• Ripretinib is 'indicated for the treatment of adult patients with advanced GIST who have received three or more kinase inhibitors, including imatinib' • MHRA approved ripretinib on 21st 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	• Oral administration • Licensed dose is 150 mg ripretinib (3 x 50 mg tablets) taken once daily* • Continue as long as benefit is observed or until unacceptable toxicity
Price	• List price £18,400 for 30-day supply (based on 3 x 50 mg tablets once daily) • Patient Access Scheme has been approved

*Committee can only recommend a drug within its marketing authorisation

Abbreviations: GIST: gastrointestinal stromal tumour; MHRA: medicines and healthcare products regulatory agency; KIT, proto-oncogene receptor tyrosine kinase; PDGFRA: platelet derived growth factor receptor alpha

History of ripretinib appraisal

TA881
May 2023

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

ID6496
January 2025

Review of TA881:

- Updated evidence submission from company
- Updated submissions from experts

ID6496
October 2025

Committee to evaluate cost-effectiveness of ripretinib based on updated company submission (clinical evidence similar to TA881):

- Slide deck focuses on company's updated submission

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Abbreviations: GIST: gastrointestinal stromal tumour

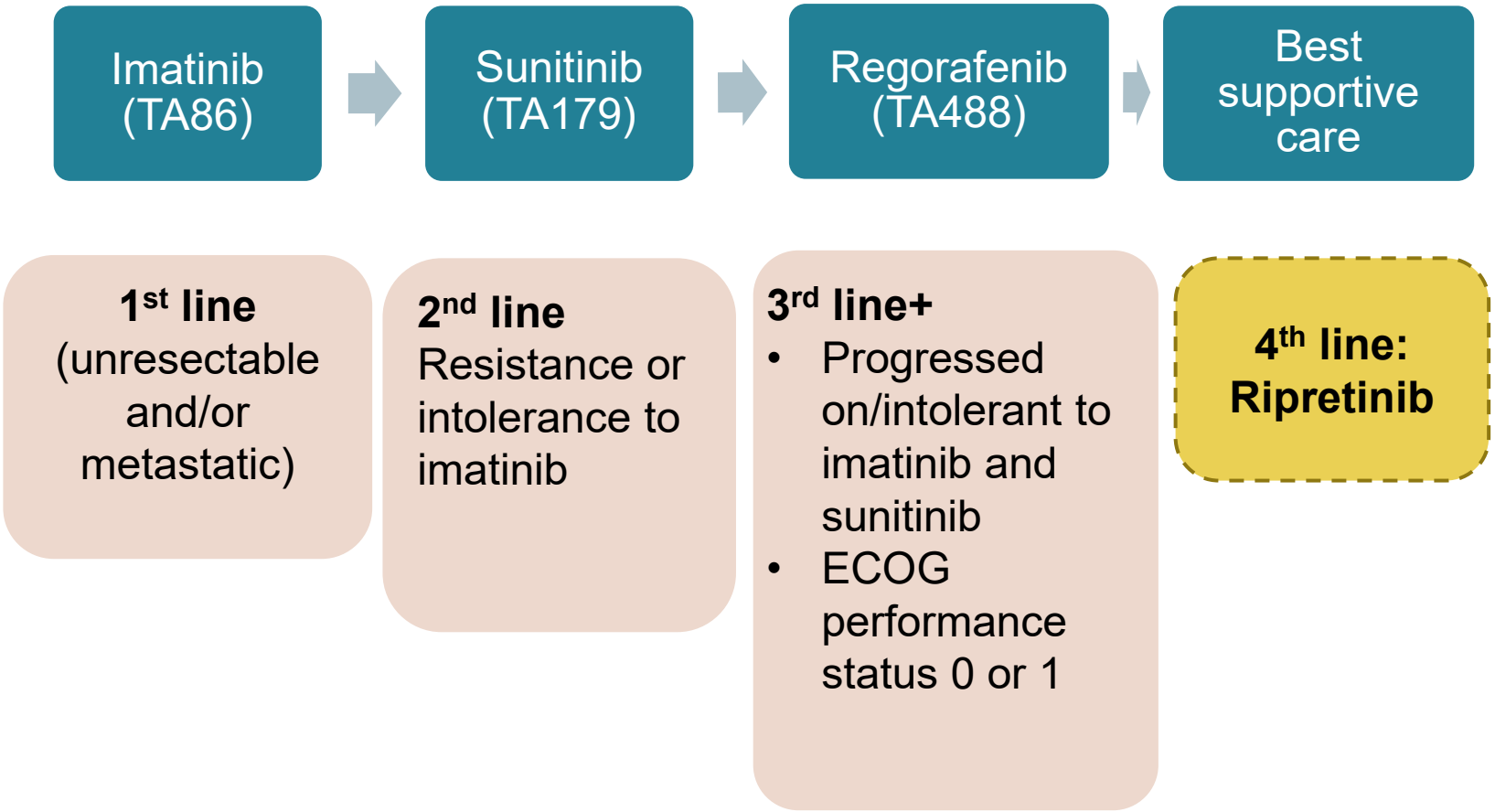
Recommendations from TA881

Committee preferred assumption TA881	Company's updated modelling in ID6496 in their updated base case	Resolved?
Stopping rule at disease progression should be removed	Does not include stopping rule allow for continued treatment (ripretinib 150 mg BID) after disease progression	Yes
OS estimates should be adjusted to account for dose escalation and treatment switching in INVICTUS	Base case does adjust OS in ripretinib group	Partly – see key issues
Drug wastage for ripretinib (0.25 of pack per person) should be included	Included drug wastage (0.25 of a pack per person) at clarification	Yes
Scenario analyses: utility values (INVICTUS) and EAG (GRID study)	Base case includes utility values from INVICTUS but explored GRID study utility value in scenario analysis	Partly - scenario analyses provided (see other issues)

Abbreviations: BID, twice daily dosing; OS, overall survival;

Treatment pathway

Figure: Current and proposed treatment pathway



Treatment options

- Initial treatment is with surgery but approximately 40% to 90% who have surgery have recurrence or metastasis.
- Currently no pharmacological treatment is recommended for GIST progressed after 3rd line treatment.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GIST: gastrointestinal stromal tumour; KIT, proto-oncogene receptor tyrosine kinase; PDGFRA: platelet derived growth factor receptor alpha

Background to disease

Causes

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

Epidemiology

- Median age at diagnosis: 60 to 65 years with an incidence of 1.5 out of every 100,000 people and approximately 900 to 1,000 new cases of GIST per year in the UK.

Classification

- Approximately 80% of cases have a mutation in KIT.
- Approximately 5% to 10% have a mutation in PDGFRA.

Abbreviations: GIST: gastrointestinal stromal tumour; KIT, proto-oncogene receptor tyrosine kinase; PDGFRA: platelet derived growth factor receptor alpha

Patient perspectives

Submissions from GIST, UK and PAWS-GIST and Sarcoma, UK

- **Current medicines** for GIST taken orally and self-administered, and most people carry on normal life. Options are limited when GIST is no longer sensitive to current treatment. Taking part in clinical trials have uncertain outcomes which can be hard to cope with.
- **Side effects of current treatments include** nausea, diarrhoea, skin rashes, sore hands and feet. Biological intolerances to TKIs can include damage to kidney or liver function.
- **There is a significant population who do not have effective treatment** because the treatment does not target the mutation, or if progression causes current treatment to be ineffective.
- **Ripretinib is a tried and tested drug** with proven efficacy against Exon 17/18 mutations. It is well tolerated giving a much better quality of life. It will also benefit people who are not able to tolerate the previous drugs.
- **Ripretinib side-effects include** hair loss which other TKIs don't exhibit. But these are a small price to pay and acceptable compared to the alternative option.

"Living with the knowledge that a third line treatment can stop working and that there are no further approved treatment options is terrifying"

"It can sometimes feel like we are forgotten about, so the chance to have access to a new drug that is proven to extend life, feels like the opportunity to redress some of this imbalance"

Abbreviations: GIST: gastrointestinal stromal tumour; PAWSD-GIST, paediatric, adolescent, wild-type & syndromic GIST; TKI, tyrosine kinase inhibitor

Clinical perspectives

Submissions from Consultant Oncologist

- **Standard treatment** is imatinib, sunitinib and regorafenib. But cardiovascular side effects means some people with pre-existing cardiovascular disease may not be able to have or tolerate these treatments at the best anti tumour dose.
- **There is an unmet need** for people with GIST that are progressing after 3 or more lines of therapy. Ripretinib after 3 or more treatments would make a significant difference as the only other option is supportive care.
- Mutational analysis of the KIT gene has allowed us to **pinpoint people who are most likely to benefit from ripretinib.**
- **The side effect profile of ripretinib** is similar to other tyrosine kinase inhibitors and manageable with patient education and input from GIST clinicians and specialist nurses.

"Ripretinib would make a significant difference as a treatment option. It meets an unmet need for people in the 4th line setting who currently have no other treatment options available"

"I have had direct clinical experience of many patients receiving ripretinib as part of an expanded access scheme. Ripretinib is well tolerated and people have had prolonged clinical benefit remaining on treatment for a long period of time with maintained quality of life"

NICE

Abbreviations, GIST, gastrointestinal stromal tumour; KIT, proto-oncogene receptor tyrosine kinase

Equalities and health inequalities

Equalities:

- One patient group stated the main equality issue is that ripretinib is available for treating GIST in other parts of the world (including Europe, America, Australia) but is not yet available to patients in the UK

Note as of July 2025 SMC accepted ripretinib for use within NHS Scotland

NICE comment: this would not normally be considered an equalities issue for the committee to address within its recommendation.

Health inequalities:

- One patient group states health inequalities issues that should be considered:
    - Social deprivation has an impact on survival.
    - GIST patients in England diagnosed from 2013 to 2017 in fifth deprivation quintile are more likely to die of disease than those in least deprived group ($p<0.1$ weak evidence).
    - GIST patients present through an emergency route as deprivation increases.
    - Many people with GISTs often reported difficulties in getting the correct referral to a sarcoma specialist centre.

NICE comment: no other evidence presented about health inequalities in this topic

Abbreviations; GIST, gastrointestinal stromal disease; SMC, Scottish Medicines Consortium

Key issues

Key issues (numbering does not align with EAG report)	Resolved?	Impact
1. Uncertainty about the long-term benefits of ripretinib on overall survival, including the effects of BID dosing: a) Should OS be adjusted with or without re-censoring? b) Should the log-normal or log-logistic extrapolation be used? What are the most plausible clinical OS estimations?	No: for discussion	Large
2. Not including evidence from a later data-cut of INVICTUS in the economic model • Should OS data from the later data-cut be incorporated into the company's economic model?	No: for discussion	Unknown

Other issue	Resolved?
Utilities • Should health state utility values from INVICTUS or the GRID trial be applied?	No but small impact

Abbreviations; BID, twice daily; OS, overall survival

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments

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INVICTUS study design

Adults with advanced GIST after 3 or more treatments and ECOG PS of 0 to 2

Randomisation 2:1; stratification 3 vs ≥ 4 and ECOG PS 0 vs 1 or 2 (n=129)

Ripretinib 150 mg 1 x daily plus BSC (n=85)

Placebo plus BSC (n=44)

Disease progression by BICR/ unblinding

Open label ripretinib (n=63)
- Escalate to 150 mg 2 x daily (n=44) or
- Continue on same dose or stop ripretinib (n=19)

- Cross over to ripretinib 150 mg 1 x daily (n=30) or
- Stop taking part in study

Disease progression

- Escalate to 150 mg 2 x daily (n=16)
- Continue on same dose or stop ripretinib

- Primary analysis, all efficacy and safety endpoints based on double-blind period
- Overall survival analysed for full study period, including double-blind and open-label periods
- Numbers based on January 2021 participant flow

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST: gastrointestinal stromal tumour;

See appendix to INVICTUS trial characteristics and treatment switching participant flow at May 2019

INVICTUS trial results – Progression free survival

Ripretinib (n=85) significantly improved progression-free survival compared with placebo (n=44)

Progression free survival in INVICTUS double-blind analysis (ITT population)			
	Median PFS in months		
	May 2019	March 2020	January 2021
Ripretinib (n=85)	6.3	6.3	6.3
Placebo (n=44)	1.0	1.0	1.0
HR (95% CI)	0.15 (0.09 to 0.25) p<0.0001	0.16 (0.10 to 0.27) p<0.0001	0.16 (0.10 to 0.27) p<0.0001

Progression free survival in INVICTUS in people crossing over from placebo to ripretinib QD and in people dose escalating to ripretinib BID (unadjusted)			
	Median PFS in months		
	DCO not reported	August 2020 (PFS1)	August 2020 (PFS2)
Crossover placebo to ripretinib 150mg QD (n=29)*	4.6		
Dose escalation ripretinib 50mg QD to BID (n=44)*		4.6	3.7

*Time from starting ripretinib to disease progression or death. Licensed dose of ripretinib is 150mg QD

BID, twice daily; CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression free survival, QD, once daily

INVICTUS trial results – Overall survival

Ripretinib (n=85) improved OS compared with placebo (n=44)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NE, OS, overall survival, QD, once daily

Overall survival in INVICTUS (ITT population; unadjusted for switching)				
	Median OS in months			
	May 2019	March 2020	January 2021	May 2022 *
Ripretinib	15.1	Not reached	18.2	[redacted]
Placebo	6.6	6.3	6.3	[redacted]
HR (95% CI)	0.36 (0.21 to 0.62)	0.42 (0.26 to 0.67)	0.41 (0.26 to 0.65)	[redacted]

OS using May 2022 data-cut is not used in the economic model * data converted from median in weeks to months

Overall survival in people crossing over from placebo to ripretinib 150 mg QD (unadjusted)		
	Median OS in months (95%CI)	
	May 2019	January 2021
Crossover placebo to ripretinib 150mg QD (n=29)	11.6	[redacted]
Did not crossover placebo to ripretinib 150mg (n=14)	1.8	[redacted]

see appendix – for KM plot of overall survival (ITT Population, May 2022)

INVICTUS trial results – Overall survival after dose escalation post-hoc analyses

Effect of post-progression dose escalation on OS is inconclusive

Abbreviations: BID twice daily, OS, overall survival; QD, once daily; MA: Marketing authorisation

Company:

- Carried out 4 analyses and sought clinical opinion to consider effect of dose escalation (BID compared with QD dosing after disease progression).
- Noted uncertainty in impact of ripretinib dose escalation on OS in INVICTUS. Each method had differing results, no clear trend.
- A two-stage adjustment estimated the effect of people switching to BID dosing in people randomised to ripretinib QD in INVICTUS (n=85).

EAG:

- Effect of post-progression dose escalation on OS is unclear, but two-stage approach is most appropriate.
- Clinicians stated they would use BID dosing where clinically appropriate if commissioning route allowed.

NHS England:

- Indicate they "would commission BID escalation as long as financial impact had been taken into account by committee".

NICE:

- Committee can only make a recommendation within the MA
- Scenarios presented showing results of BID escalation but not in company or EAG base case.

See EAG critique of company's analyses, Naïve comparison (unadjusted); Censored analyses; Cox proportional hazards time-varying analysis; Survival probability INVICTUS- did and did not dose escalate;

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- ✓ **Modelling and cost effectiveness**
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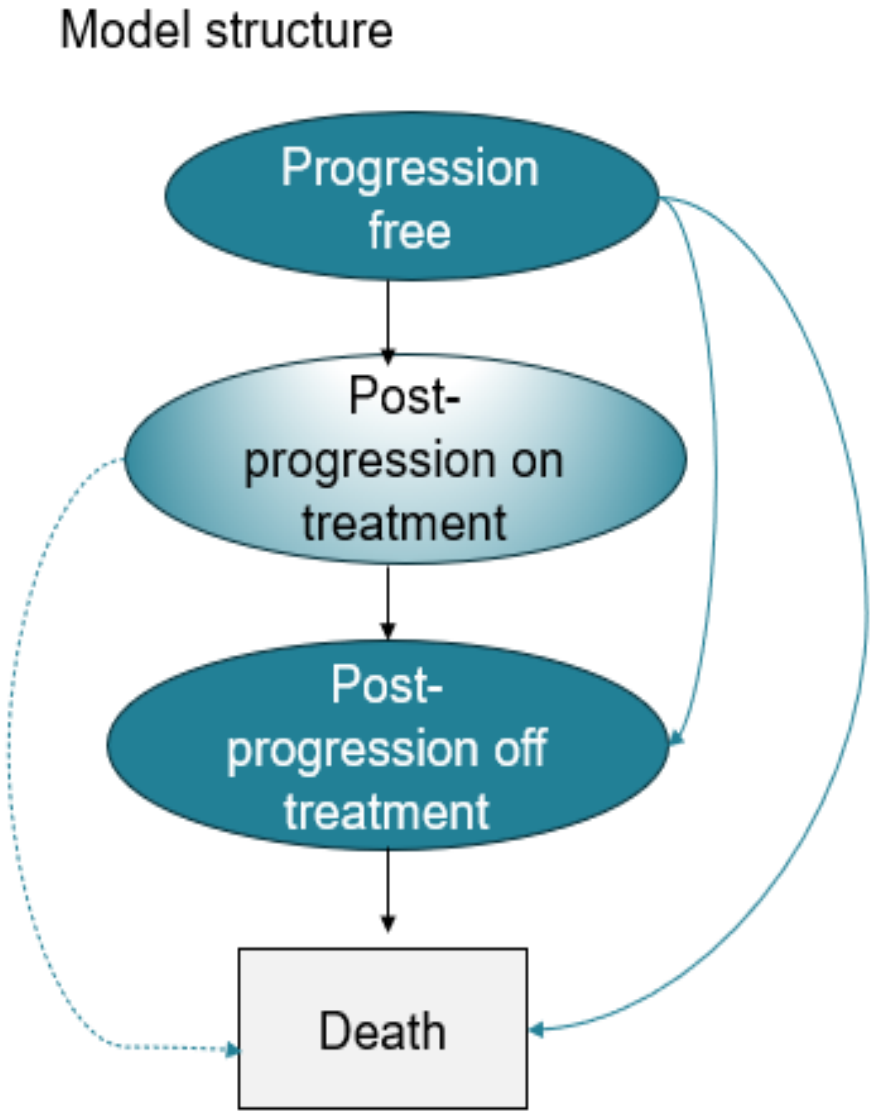
Company's model overview



Technology affects **costs** by increasing:

- overall costs (acquisition of ripretinib)
- overall disease management costs (extended overall survival)

Technology affects **QALYs** by:

- Extending PFS and OS and decreasing HRQoL (slightly) due to burden of adverse events

Assumptions with **greatest ICER effect**:

- Adjustment using the two-stage estimation method with re-censoring leads to higher ICERs compared with the equivalent adjustment models excluding re-censoring.

NICE see appendix – for how company incorporated evidence in economic model

Abbreviations HRQoL, health related quality of life; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year

Key issue 1a: Uncertainty in long-term benefits of ripretinib on OS (1) Impact of recensoring in adjustment of BID dosing on OS results

Large impact

Background

- In INVICTUS people could have same dose (QD) or higher dose (BID) of ripretinib at progression.
- EAG and company agree to adjust ripretinib arm for impact of BID dosing
  - Note, company agreed to adjustment after the EAG report was submitted ("updated analyses")

Company updated base case after EAG report	EAG base case
• 2-stage adjustment with complex generalised gamma • Log-normal extrapolation • Without recensoring	• 2-stage adjustment with complex generalised gamma • Log-logistic extrapolation • With recensoring

Company's updated analyses:

- Both censoring and non-censoring approaches explored (with recensoring, follow-up is shorter and has a steep drop) impacting on long-term extrapolations largely driven by a drop in number of people at risk (next slide)

EAG

- Re-censoring can reduce bias. But longer-term data can be lost, creating uncertainty in extrapolations
- More mature follow-up would provide greater confidence in the extrapolation and clinical plausibility
- Smoothed hazard of KM for OS without re-censoring suggests an initial hazard increase is followed by a later hazard increase (slide 22)

Should OS be adjusted with or without re-censoring?

Abbreviations: BID, twice daily; KM, Kaplan Meier; OS, overall survival; QD, once daily;

Key issue 1a: Uncertainty in long-term benefits of ripretinib on OS (2) Impact of recensoring in adjustment of BID dosing on OS results

Large impact

Kaplan-Meier plot of time from randomisation to death in people randomised to ripretinib QD (N=85) Impact of re-censoring of counterfactual survival times in two-stage estimation adjustment for IPDE (from company updated addendum)

NICE

Abbreviations: BID, twice daily; CF, counterfactual; IPDE, Intrapatient dose escalation; QD, once daily;

Key issue 1a: Uncertainty in long-term benefits of ripretinib on OS (3) Impact of recensoring in adjustment of BID dosing on OS results

Large impact

Empirical and modelled hazard functions based on the complex 2-stage estimation BID-adjustment (generalised gamma) without re-censoring

EAG

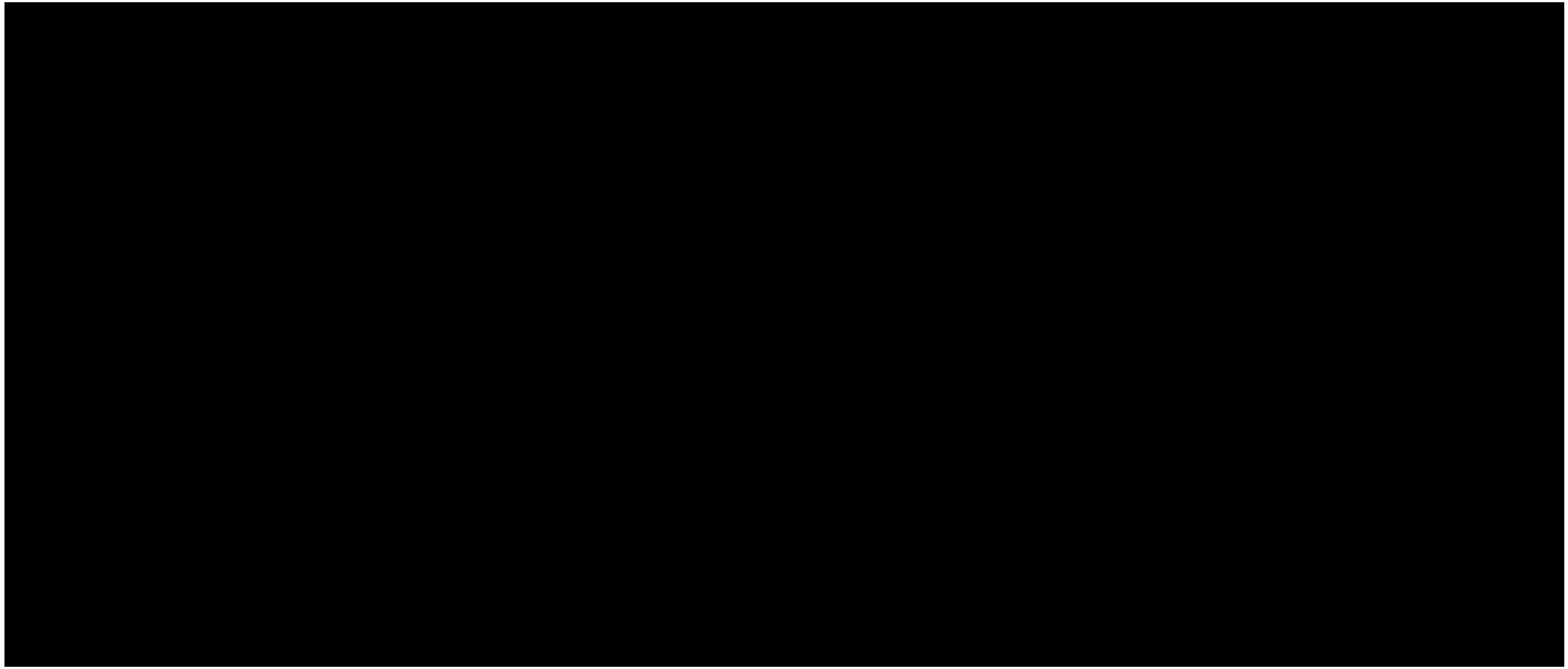
- None of the extrapolation models provide a satisfactory fit to capture the timing of the first hazard increase in the two-stage adjusted data without re-censoring
- Log-logistic model provides a better fit than log-normal model, but overall fit is still sub-optimal

Abbreviations: BID, twice daily; CF, counterfactual; OS, overall survival

Large impact

Key issue 1a: Uncertainty in long-term benefits of ripretinib on OS (4) Impact of recensoring in adjustment of BID dosing on OS results

Empirical and modelled hazard functions based on the complex 2-stage estimation BID-adjustment (generalised gamma) with re-censoring



NICE

Abbreviations: BID, twice daily; OS, overall survival

Key issue 1b: Uncertainty in long-term benefits of ripretinib on OS (1) Model predictions of OS and long-term clinical plausibility

Small impact

Background:

- Company's UK advisory board (2024) n=[redacted] predict clinical estimates between 1% to 8% but stated that [redacted] was based on a future care pathway.
- Consensus view was that an estimated 10-year OS probability of [redacted] is more realistic

Company base case (updated since submission)	EAG base case
• 2-stage adjustment with complex generalised gamma, log-normal extrapolation, without recensoring • 10-year OS probability using log-normal: [redacted]	• 2-stage adjustment with complex generalised gamma, log-logistic extrapolation, with recensoring • 10-year OS probability using log-logistic [redacted]

EAG:

- Company's initial 10-year OS probability before updated submission was [redacted]
- Updated base case model results in a more optimistic 10-year OS than the consensus estimate of its consulted clinical advisors.
- EAG's clinical advisors consider ripretinib after disease progression will lead to additional OS benefits in 4L+ setting, likely most BSC-patients die by 1.5 years.

What are the most plausible clinical OS estimations?

Abbreviations: OS, overall survival

Small impact

Key issue 1b: Uncertainty in long-term benefits of ripretinib on OS (2)

Modelled OS predictions in company's previous and updated base case and EAG preferred analysis, (generated by the EAG using the company's model)

Abbreviations: BSC, best supportive care; OS, overall survival;

Key issue 2: Uncertainty generated by not using a later data-cut of INVICTUS OS data in the economic model

Uncertain impact

Background

TA881	ID6496 submission	Clarification
• January 2021 data cut	• January 2021 data cut	• Company confirmed May 2022 data cut is available for OS and safety data

Company

- Analysis began before 2022 data was available.
- No value in integrating new data cut in model, as 2022 data is less robust than 2021 data:
  - Prespecified end of study analyses only included OS and safety so including other clinical inputs is heterogenous.
  - Using open-label setting after switching and dose escalation increases risks and biases from drop-out and other biases associated with data collection.

EAG

- Despite limitations during the unblinded period, long-term follow-up data provide valuable insights.
- OS is a hard endpoint and less susceptible to subjective influences so would allow re-censoring in the 2-stage dose-escalation scenario in line with TSD recommendations.
- Recognised re-doing all adjustment and survival analyses may not have been feasible in timescales.

Should OS data from the later data cut be included in the economic model?

Abbreviations: HRQOL, health related quality of life; OS, overall survival; PFS, progression free survival; TSD, technical support document TTD, time to treatment discontinuation

Other issue: Utilities

Abbreviations: BSC, best supportive care HRQOL, health related quality of life; ICER, incremental cost-effectiveness ratio; PD, progressed disease

Small impact

Background

- In TA881: Company base case includes utility values from INVICTUS mapped to EQ-5D-3L. EAG applied GRID trial PD utility. Committee requested scenario analysis exploring impact

Company

- Initial and revised base case based on utility values in INVICTUS. GRID utility explored in scenario analysis

Health state utility values in company base case

Health state	Mean utility (SD)		Source
	Ripretinib	BSC	
Progression-free	0.722 (0.217)		EQ-5D-5L estimates from INVICTUS (mapped to 3L; Hernández Alava)
Progressed disease (on treatment)	0.699 (0.218)	0.624 (0.284)	
Progressed disease (off treatment)	0.624 (0.284)		

EAG comments

- HRQoL estimates for people having ripretinib after progression for both treatment arms. It may have included people who did not switch to ripretinib after progression
- EAG clinical advice consider utility values in company model health states plausible
- Using alternative utility value for PD (off treatment/BSC) state based on GRID (0.647) has minimal effect on the ICER

Should health state utility values from INVICTUS or the GRID trial be applied?

Summary of company and EAG base case assumptions

Key assumptions in company and EAG base case. Both apply 1.7 QALY weighting for severity

Assumption	Company updated base case	EAG base case	Notes
Data informing model	Uses January 2021 data cut from INVICTUS but note May 2022 data cut of INVICTUS OS data is available		EAG: relying on 2021 data cut increases uncertainty in OS modelled estimates for ripretinib
Adjustment beyond progression and OS parametric extrapolation	Use two-stage adjustment with complex generalised gamma without re-censoring; log-normal extrapolation	Use two-stage adjustment with complex generalised gamma with re-censoring; log-logistic extrapolation	• Company: OS predicted probability at 10 years of [redacted] • EAG: OS predicted probability at 10 years of [redacted]
Ripretinib 150 mg costs	• Costs of QD dosing only	• Costs of QD dosing in preferred base case in line with licensed dose	• EAG alternative scenario analyses if QD only or BID dosing is commissioned • BID dosing for proportion in INVICTUS decreases ICER

Managed access

- Company has not submitted a managed access proposal. Committee can make a recommendation with managed access if:
  - technology cannot be recommended for use because evidence is too uncertain
  - technology has **plausible potential** to be cost effective at **currently agreed price**
  - new evidence that could **sufficiently support case for recommendation** is expected from clinical trials, or could be collected from people having it in clinical practice
  - data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

Company base case results based on company's updated analyses

All cost-effectiveness results include the company's PAS discount and apply a 1.7 QALY weighting for severity (EAG and company agree)

Deterministic incremental base case results

Option	LYGs	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's updated base case model, BID-adjusted OS for ripretinib group, 2-stage, complex model generalised gamma without re-censoring, log-normal							
Ripretinib	2.90	[redacted]	[redacted]	2.59	[redacted]	[redacted]	**£29,350**
BSC	0.31	[redacted]	[redacted]	-	-	-	-

* undiscounted

Probabilistic incremental base case results

Option	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
Company's updated base case model, probabilistic					
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	**£30,232**
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-

Life years not reported for probabilistic results

NICE

Abbreviations; BID, twice daily; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year;

Company's scenario analyses - unadjusted for BID dosing based on company's updated analyses

Alternative OS models unadjusted for BID dosing, includes BID dosing costs (50%)

	Inc. QALYs	Inc. Costs	ICER
Exponential	[redacted]	[redacted]	£35,332
Weibull	[redacted]	[redacted]	£36,476
Gompertz	[redacted]	[redacted]	£26,339
Log-normal	[redacted]	[redacted]	£26,676
Log-logistic	[redacted]	[redacted]	£27,382
Generalised gamma	[redacted]	[redacted]	£27,847

Alternative OS models unadjusted for BID dosing, includes BID dosing costs (60.1%)

	Inc. QALYs	Inc. Costs	ICER
Exponential	[redacted]	[redacted]	£36,196
Weibull	[redacted]	[redacted]	£37,371
Gompertz	[redacted]	[redacted]	£26,964
Log-normal	[redacted]	[redacted]	£27,310
Log-logistic	[redacted]	[redacted]	£28,035
Generalised gamma	[redacted]	[redacted]	£28,513

Abbreviations; BID, twice daily; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year;

EAG preferred base case results

Deterministic incremental base case results

Option	LYGs	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
EAG-preferred analysis BID-adjusted OS for ripretinib group; 2-stage, complex model with re-censoring, log-logistic;							
Ripretinib	1.79	[redacted]	[redacted]	1.47	[redacted]	[redacted]	**£44,964**
BSC	0.31	[redacted]	[redacted]	-	-	-	-

* undiscounted

Probabilistic incremental base case results

Option	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
EAG-preferred analysis BID-adjusted OS for ripretinib group; 2-stage, complex model with re-censoring, log-logistic;					
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	**£47,162**
BSC	[redacted]	[redacted]	-	-	-

Life years not reported for probabilistic results

Abbreviations; BID, twice daily; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life year gained; OS, overall survival; QALY, quality-adjusted life year

EAG's additional analyses

Additional analyses of company's updated base-case including log-logistic OS extrapolation for ripretinib, as EAG notes no justification for preferring log-logistic to the log-normal

Deterministic incremental results

Option	LYGs	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (incl. DM)
Ripretinib	2.93	[redacted]	[redacted]	2.62	[redacted]	[redacted]	**£29,717**
BSC	0.31	[redacted]	[redacted]	-	-	-	-

Abbreviations; BID, twice daily; QALY, quality-adjusted life year

EAG's alternative scenario analyses 1

Alternative OS models of EAGs preferred analyses: unadjusted for BID dosing, includes BID dosing costs for 60.1% of post-progression time

	Inc. QALYs	Inc. Costs	ICER
Exponential	[redacted]	[redacted]	**£36,196**
Weibull	[redacted]	[redacted]	**£37,371**
Gompertz	[redacted]	[redacted]	**£26,964**
Log-normal	[redacted]	[redacted]	**£27,310**
Log-logistic	[redacted]	[redacted]	**£28,035**
Generalised gamma	[redacted]	[redacted]	**£28,513**

Abbreviations; BID, twice daily; LYG, life year gained;; OS, overall survival; QALY, quality-adjusted life year;

EAG's alternative scenario analyses 2

Alternative OS models of EAGs preferred analyses: adjusted for BID dosing (generalised gamma, with re-censoring) includes QD dosing costs only (ASA2)

	Inc. QALYs	Inc. Costs	ICER
Exponential	[redacted]	[redacted]	**£48,123**
Weibull	[redacted]	[redacted]	**£61,678**
Gompertz	[redacted]	[redacted]	**£62,682**
Log-normal	[redacted]	[redacted]	**£41,452**
Log-logistic	[redacted]	[redacted]	**£44,964**
Generalised gamma	[redacted]	[redacted]	**£61,872**

Abbreviations; BID, twice daily; LYG, life year gained;; OS, overall survival; QALY, quality-adjusted life year; QD, once daily

EAG's alternative scenario analyses 3

Alternative OS models of EAGs preferred analyses: adjusted for BID dosing (generalised gamma, without re-censoring) includes QD dosing costs only (ASA3)

	Inc. QALYs	Inc. Costs	ICER
Exponential	[redacted]	[redacted]	**£38,461**
Weibull	[redacted]	[redacted]	**£38,865**
Gompertz	[redacted]	[redacted]	**£18,835**
Log-normal	[redacted]	[redacted]	**£29,350**
Log-logistic	[redacted]	[redacted]	**£29,717**
Generalised gamma	[redacted]	[redacted]	**£25,856**

Highlighted row reflects EAG equivalent scenario but excluding re-censoring

Abbreviations; BID, twice daily; LYG, life year gained;; OS, overall survival; QALY, quality-adjusted life year; QD, once daily

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments

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

NICE National Institute for Health and Care Excellence

Key issues

Key issues (numbering does not align with EAG report)	Resolved?	Impact
1. Uncertainty about the long-term benefits of ripretinib on overall survival, including the effects of BID dosing: a) Should OS be adjusted with or without re-censoring? b) Should the log-normal or log-logistic extrapolation be used? What are the most plausible clinical OS estimations?	No: for discussion	Large
2. Not including evidence from a later data-cut of INVICTUS in the economic model • Should OS data from the later data-cut be incorporated into the company's economic model?	No: for discussion	Unknown

Other issue	Resolved?
Utilities • Should health state utility values from INVICTUS or the GRID trial be applied?	No but small impact

NICE

Abbreviations; BID, twice daily; OS, overall survival

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments

Supplementary appendix

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INVICTUS trial characteristics

*link

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 stop or continue with current or double dose), or unacceptable toxicity
Comparator	Placebo plus best supportive care (can stop or switch to ripretinib on disease progression)
Duration	• Primary data-cut: May 2019 (median 6.3 months follow-up) • Additional follow-up after 9 months (August 2020) and 19 months (January 2021) • Additional follow-up (May 2022) has not been used in the economic analyses
Primary outcome	Progression-free survival assessed by blinded independent central review
Secondary outcome	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 participant flow

*link

Participant flow in INVICTUS and proportions still on treatment, May 2019 (reproduced from TA881)

	Ripretinib	Placebo group
Randomised	85	44
Did not have treatment	0	1 (2%)
Still on double-blind treatment	26 (31%)	1 (2%)
Stopped double-blind treatment	17 (20%)	13 (30%)
Moved to open-label ripretinib (150mg QD or 150mg BID)	42 (49%)	29 (66%)
Still having open-label ripretinib	10 (12%)	11 (25%)
Stopped open-label ripretinib	32 (38%)	18 (41%)
Total still having ripretinib	36 (42%)	11 (25%)
Total stopped or not received ripretinib	49 (58%)	33 (75%)

INVICTUS trial results – Overall survival ITT population (May 2022 data cut- Not included in economic analyses)

Company: overall, the median OS for each treatment arm using the May 2022 data-cut is the same as for the January 2021 data-cut.

Kaplan-Meier plot of overall survival (ITT Population, as of 11 May 2022)

*link

Abbreviations: BICR, blinded independent central review; BID, twice daily; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression free survival, QD, once daily

Impact of dose escalation after progression on OS results

link

Analysis	Variation	EAG critique
Censored BID-dosing	Unadjusted OS in ripretinib arm compared with OS in ripretinib arm in people censored at start of BID dosing	Censored analysis improved OS, suggests excluding BID dosing leads to better outcomes. Contradicts company and EAG clinical advice
	People with disease progression escalated to BID, combined with people without disease progression Compared with people with disease progression who did not escalate to BID, combined with people without disease progression	Subject to selection bias and cannot provide causal relationships
Cox proportional hazards time-varying analysis	Model 1:Only ripretinib IPDE as time-varying covariates Model 2: Ripretinib IPDE, progression status, ECOG, EQ-5D VAS, lesion diameter sum, and percent change from baseline as the time-varying covariates Model 3: All covariates in Model 2, as well as time varying covariates: Baseline lesion diameter sum, age, sex, race, region, baseline BMI, hepatic impairment, number of prior therapies, creatinine clearance, baseline renal impairment	Counterintuitive estimates because causal methods such as marginal structural models were not applied so did not adequately address time-varying confounding. Suggests BID dosing harmful and contrasts with clinical expectations.
Two-stage adjustment	Simple model: adjusted for time to progression Complex model: adjusted for time to progression, ECOG performance status at progression, EQ-5D VAS score at progression, and baseline age	Updated 2 stage (after clarification) is in line with TSD 16 and 24 included complex model in EAG preferred analyses

INVICTUS trial results – Overall survival after dose escalation post-hoc analyses

Link

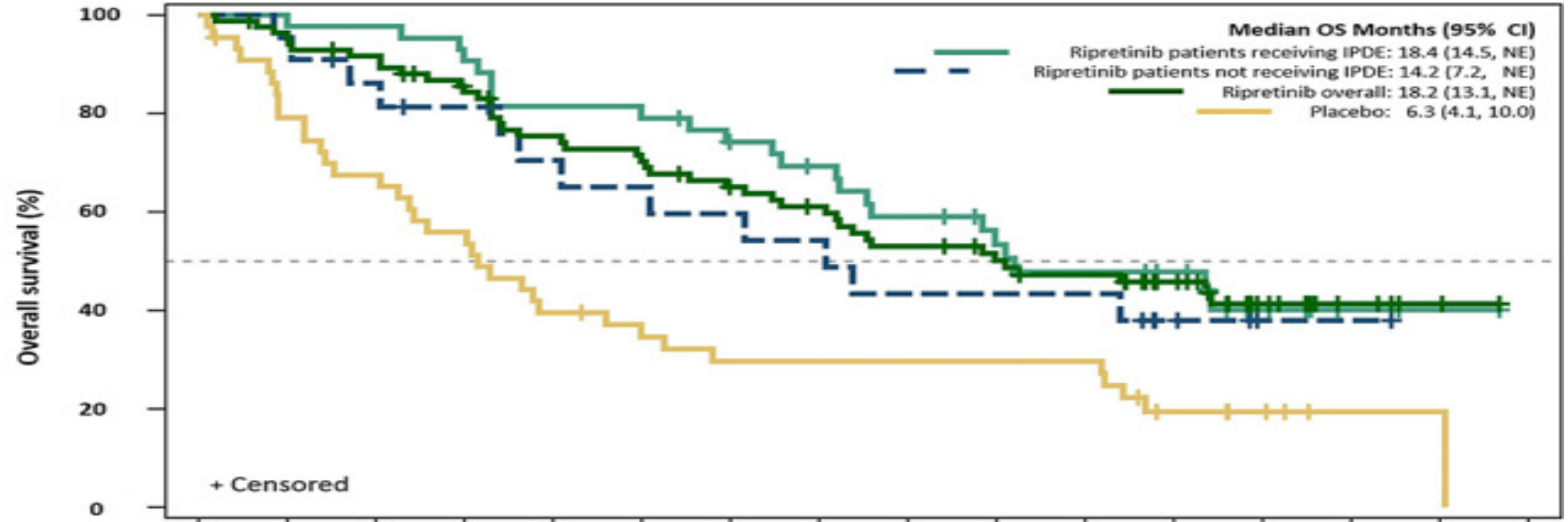
Analysis	Effect of dose escalation	Considerations
Open-label BID vs QD OS analysis	Considerable (+4.5 months median OS), positive effect	Likely overestimated effect for BID in the absence of adjustment for treatment effect modifiers, specifically ECOG PS
BID censoring analysis	Negligible, negative effect	Result is likely to include bias associated with informative censoring and loss of data over time
Cox proportional hazards time-varying analysis	Considerable (40% increase in risk of death), negative effect	Does not seem clinically realistic given the safety profile of BID dosing; suggests that another (uncontrollable) treatment effect modifier drove the choice to dose escalate
Two-stage adjustment	Uncertain, positive effect	Assumes no time-dependent confounding between time of progression and time of treatment switch
Clinicians (UK advisory board)	Unquantifiable, positive effect	Available data are insufficient to estimate effect size

INVICTUS trial results – Overall survival after dose escalation post-hoc analyses

link

link

KM OS estimates INVICTUS (August 2020):
Naïve comparison: People who did and did not dose escalate



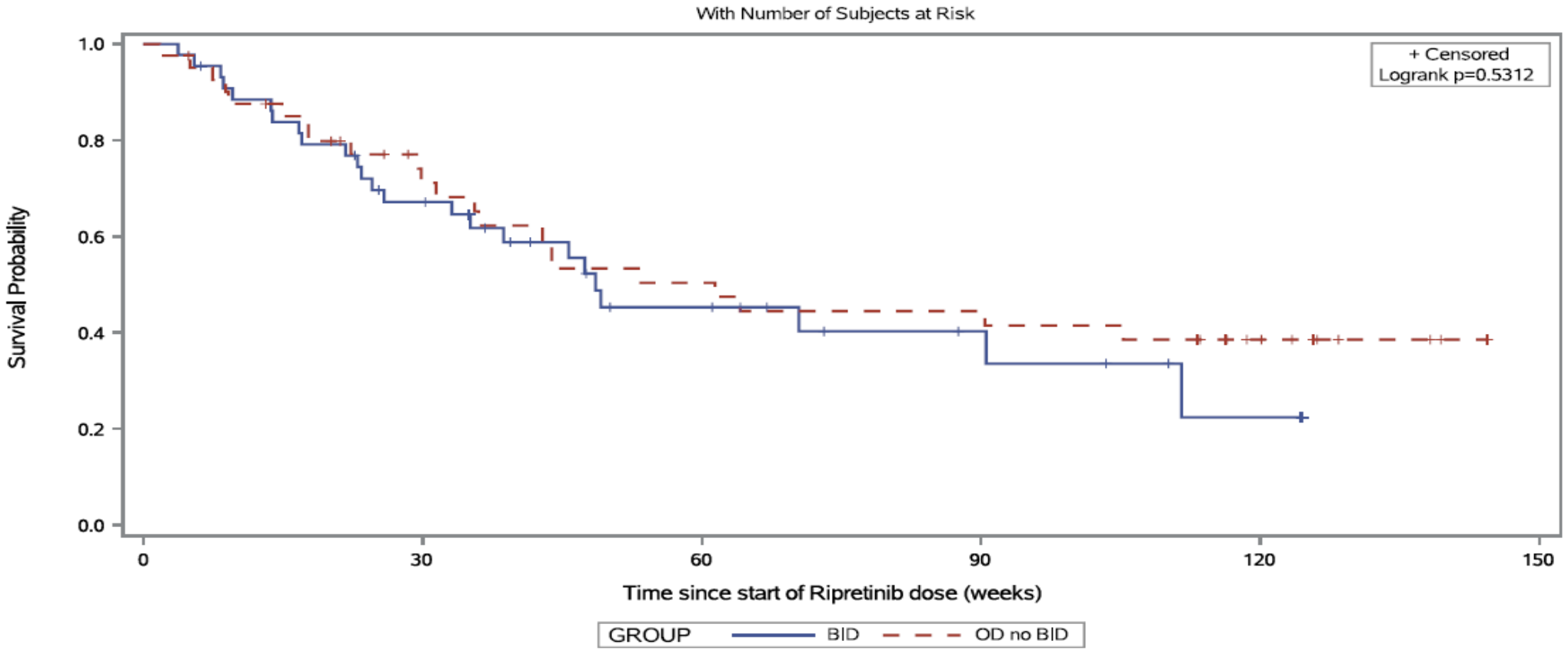
Number at risk:																
Ripretinib patients receiving IPDE	43	43	42	39	35	34	30	27	23	19	16	14	7	2	1	0
Ripretinib patients not receiving IPDE	22	21	18	16	13	12	11	10	8	8	8	4	1	1	0	0
Ripretinib overall	85	81	76	67	59	55	49	45	39	35	32	24	12	5	2	0
Placebo	44	34	29	24	17	14	12	12	12	12	12	6	4	1	1	0

INVICTUS trial results – Overall survival after dose escalation post-hoc analyses

link

link

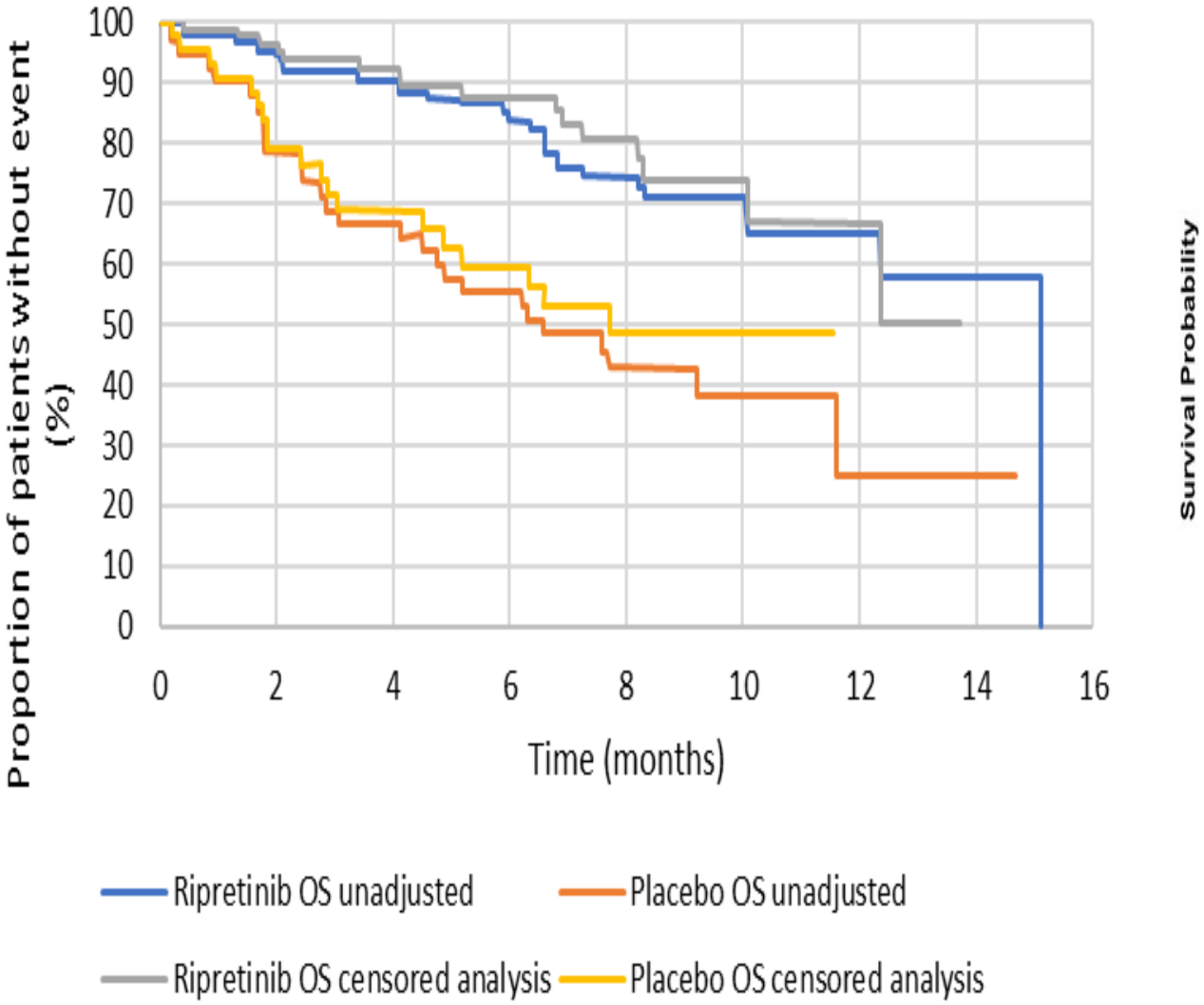
Survival probability in INVICTUS- In those who didn't dose escalate (first QD dose to death), and in those who did dose escalate (first BID dose to death)



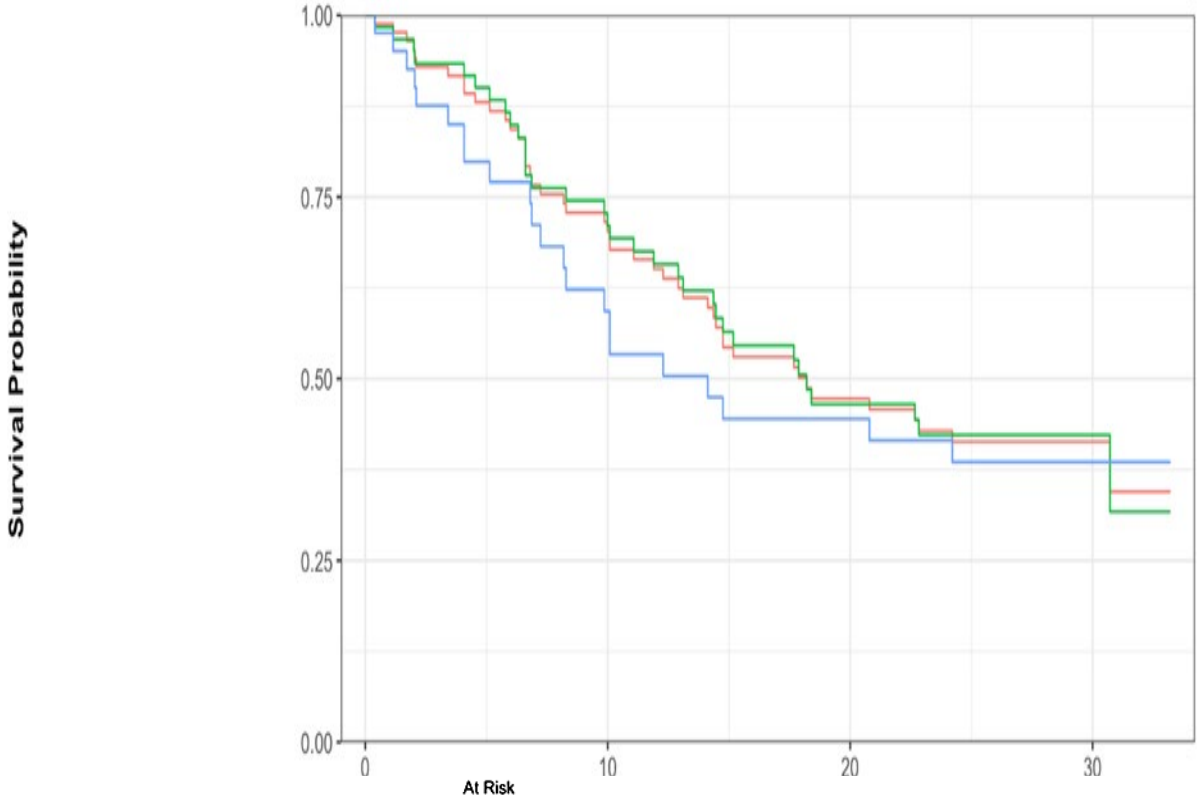
INVICTUS trial results – Overall survival after dose escalation post-hoc analyses censored analyses

link

Unadjusted OS and OS in ripretinib BID data after disease progression (censored)



Unadjusted OS and OS (censored) after disease progression



At Risk

All	85	55	32	10
Non-progressors and progressors on BID	61	41	22	8
Non-progressors and progressors on QD	41	20	15	3
Events				
All	0	24	41	45
Non-progressors and progressors on BID	0	17	30	32
Non-progressors and progressors on QD	0	15	20	22

INVICTUS trial results – Overall survival after dose escalation (2) post-hoc analyses time-varying analyses

- Company: Carried out Cox proportional hazards time-varying analysis.

link

Covariates	Hazard ratio (95% CI)
Study treatment	1.58 (0.85, 2.95) p=0.150
Study treatment, progression, ECOG, EQ-5D VAS, lesion diameter sum, lesion diameter (% change from baseline)	1.43 (0.66, 3.12) p=0.365
Study treatment, progression, ECOG, EQ-5D VAS, lesion diameter sum, lesion diameter (% change from baseline), baseline lesion diameter sum, age, sex, race, region, baseline BMI, hepatic impairment, number of prior therapies, baseline CrCl, and baseline renal impairment	1.37 (0.66, 2.84) p=0.397

Key issues: Uncertainty in long-term benefits of ripretinib on OS

Fitting parametric model: fitting process and model selection

Goodness of fit statistics for OS data

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	415.08	**417.52**	137.48	139.26	552.55	556.78
Weibull	416.92	421.81	134.72	138.29	551.64	560.10
Gompertz	416.66	421.54	137.24	140.81	553.90	562.35
Log-normal	**414.14**	419.03	134.49	138.06	548.63	557.09
Log-logistic*	414.15	419.04	**133.23**	**136.80**	**547.38**	**555.83**
Generalised gamma	416.10	423.43	135.89	141.25	551.99	564.67

*model used in company base case; bold indicates best fitting model

Goodness of fit statistics of two-stage adjustment to account for the effect of dose escalation on OS

Adjustment approach	Distribution	AIC	Survival time ratio estimate (95% CI)
Simple	Exponential	166.53	2.44 (1.19, 5.01)
	Weibull	167.78	2.68 (1.16, 6.15)
	Log-normal	**159.96**	**3.45 (1.56, 7.60)**
	Log-logistic	160.26	4.28 (1.90, 9.64)
	Generalised gamma	160.9	3.21 (1.48, 6.97)
Complex	Exponential	158.7	1.95 (0.72, 5.25)
	Weibull	160.7	1.94 (0.71, 5.34)
	Log-normal	149.51	2.40 (1.10, 5.25)
	Log-logistic	150.5	2.34 (1.03, 5.29)
	Generalised gamma	**144.51**	**2.72 (1.57, 4.74)**

Survival time ratios >1 indicate longer survival with ripretinib BID versus QD. Bold indicates best fitting model

How company incorporated evidence into model

link

Parameter	Input and evidence source
Population	Advanced GIST after 3 treatments including imatinib Baseline characteristics (INVICTUS) 60.10 years; 56.6% male at model entry
Intervention Comparator	Ripretinib administered in licensed indication and at licensed dose (150 mg QD) compared with best supportive care
Clinical parameters	INVICTUS trial fitted to parametric models • OS: modelled using independently fitted log-logistic distributions in both treatment groups includes two-stage adjustment with complex generalised gamma without re-censoring for IPDE to ripretinib 150mg BID at progression in INVICTUS; log-normal extrapolation • PFS: modelled using independently fitted log-normal distributions in both treatment groups • TTD: modelled using an exponential distribution for ripretinib
Utilities	EQ-5D-5L data collected in INVICTUS mapped to 3L version (Van Hout et al) • Same utility values for progression free (on treatment) and progressed disease (off treatment) applied in each treatment group • Utility value applied to people staying on ripretinib after progression lies between the values for the PF and PD (off treatment) states. Utility values are adjusted for increasing age.
Costs	• All post-progression ripretinib costs are based on ripretinib 150mg QD dose • Prior to disease progression, pre-treatment and disease management costs assumed to be higher for people receiving ripretinib compared with having BSC alone