Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies. A Single Technology Appraisal

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Date completed	10th August (post FAC version)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR134116.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Dr Robin Young, Sheffield Teaching Hospitals NHS Foundation Trust, and Dr Jane Hook, Leeds Teaching Hospitals NHS Trust, for clinical advice relating to this project. We would also like to thank Aline Navega Biz, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Tappenden P, Cooper K, Kearns B, Wong R, Rawdin A, Leaviss J. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies. A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2022.

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Ruth Wong critiqued the company's search strategy. Katy Cooper and Joanna Leaviss summarised and critiqued the clinical effectiveness data reported within the company's submission. Ben Kearns critiqued the company's treatment switching analysis. Paul Tappenden and Andrew Rawdin critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
4L	Fourth-line
4L+	Fourth- and subsequent-line
AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
ASA	Additional sensitivity analysis
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice a day
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMU	Commercial Medicines Unit
CR	Complete response
CS	Company's submission
CSR	Clinical Study Report
CT	Computerised tomography
cuSCC	Cutaneous squamous cell carcinoma
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMBASE	Excerpta Medica dataBASE
EoL	End of Life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item
EQ-5D-5L	EuroQol 5 dimensions 5 levels
EQ-VAS	EuroQol visual analogue scale
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
EUCTR	EU Clinical Trials Register
FBC	Full blood count
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
HCHS	Hospital and community health services
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse probability of censoring weights
IPD	Individual patient data
ITC	Indirect treatment comparison
ITCRP	International Clinical Trials Registry Platform
ITT	Intention-to-treat

LFT	Liver function test
LYG	Life year gained
MCID	Minimal clinically important difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
n	Number
N/a	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute for Health and Care Excellence
NR	Not reported
ONS	Office for National Statistics
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive/progressed disease
PDGFRA	Platelet derived growth factor receptor alpha
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PPES	Palmar-plantar erythrodysaesthesia syndrome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QD	Once a day
Q-Q	Quantile-quantile
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
RPSFTM	Rank preserving structural failure time model
RT	Radiotherapy
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Stable disease / standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical support document
TTD	Time to treatment discontinuation
TTP	Time to progression
UK	United Kingdom
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This report assesses ripretinib for the treatment of advanced gastrointestinal stromal tumours (GISTs) after at least three prior treatments. This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's preferred analysis are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are detailed in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

The key issues identified by the ERG are summarised in Table 1.

Table 1: Summary of the ERG's key issues

ID3805	Summary of issue	Report sections
Issue 1	Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	3.3 and 5.3.5 (critical appraisal point [2])
Issue 2	Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	4.2.3 and 5.3.5 (critical appraisal point [3])
Issue 3	Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced OS outcomes and implausible OS predictions given the company's stopping rule	5.3.5 (critical appraisal points [4] and [5])
Issue 4	Proposed stopping rule is not in line with existing recommendations on the use of TKIs	3.2
Issue 5	Uncertainty surrounding the level of HRQoL experienced by patients after progression on fourth-line therapy	5.3.5 (critical appraisal point [6])

OS - overall survival; TKI - tyrosine kinase inhibitor; HRQoL - health-related quality of life

The company's economic model includes a stopping rule whereby all patients discontinue ripretinib at the point of disease progression. The key differences between the company's base case analysis and the ERG's preferred model relate to how overall survival (OS) is modelled and the utility value applied in the progressed disease health state. The company's base case model applies log-normal survival models

fitted to data on OS which have been adjusted for treatment switching in the best supportive care (BSC) group and unadjusted OS data in the ripretinib group. The ERG's preferred model applies generalised gamma survival models which have been fitted to OS data which have been adjusted for post-progression ripretinib use in both treatment groups. The company's model applies utility values from INVICTUS to both the progression-free and progressed disease health states (unadjusted for post-progression ripretinib use); the ERG's preferred model applies a comparatively lower utility value to the progressed disease state obtained from the GRID trial. The ERG's preferred model also includes a cost associated with drug wastage which is not included in the company's model.

1.2 Overview of key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life (OS) and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with BSC alone, ripretinib is assumed to impact on QALYs by:

- Extending progression-free survival (PFS)
- Extending OS
- Slightly reducing HRQoL due to a higher burden of adverse events (AEs).

Compared with BSC alone, ripretinib is assumed to affect costs by:

- Increasing overall costs due to the acquisition cost of ripretinib
- Increasing overall disease management costs due to extended OS
- Increasing the costs associated with managing AEs.

The modelling assumptions that have the greatest effect on the ICER for ripretinib versus BSC are:

- Whether OS in the ripretinib group is adjusted to account for potential confounding due to the use of post-progression ripretinib in the INVICTUS trial
- The choice of parametric survival model fitted to the adjusted/unadjusted OS data
- The choice of utility value applied to the progressed disease health state.

1.3 The decision problem: Summary of the ERG's key issues

The company's submission (CS) describes the current treatment pathway for patients with advanced GIST as being comprised of first-line imatinib, second-line sunitinib, third-line regorafenib and BSC. The evidence in the CS relates to the clinical effectiveness and cost-effectiveness of fourth- or later-line ripretinib versus BSC for the treatment of patients with advanced GIST. The decision problem addressed in the CS is generally in line with the final NICE scope. The ERG's clinical advisors and the UK clinical expert consulted by the company commented that in clinical practice, many patients who

progress on third-line regorafenib continue to receive this treatment after disease progression. The company does not consider continued post-progression regorafenib to be a comparator for ripretinib (see Issue 1).

Issue 1: Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression

Report section	3.3 and 5.3.5 (critical appraisal point [2])
Description of issue and why the ERG has identified it as important	The company's economic model includes BSC as the sole comparator. The comparator listed in the final NICE scope is defined as *"established clinical management without ripretinib including best supportive care.*" The ERG's clinical advisors commented that in usual practice, many patients (50% or more) who have progressed on regorafenib (after previously failing earlier treatment with both sunitinib and imatinib) continue to receive regorafenib if they are still obtaining benefit from it, unless their disease is progressing rapidly or they are experiencing significant toxicity, and if no further treatments are available. Patients who do not receive regorafenib post-progression receive BSC alone. The ERG's clinical advisors commented that if ripretinib received a positive recommendation from NICE, they would switch patients onto fourth-line ripretinib as soon as they progress on third-line regorafenib. The ERG believes that this suggests that continued regorafenib use after progression at third-line should be considered as a comparator for ripretinib. The CS does not provide a clinical or economic comparison of fourth-line ripretinib versus continued regorafenib use after disease progression.
What alternative approach has the ERG suggested?	During the clarification round, the ERG requested that the company undertake an exploratory economic comparison of ripretinib versus continued post-progression regorafenib. However, the company did not present this comparison.
What is the expected effect on the cost-effectiveness estimates?	The relative cost-effectiveness of ripretinib versus continued post-progression regorafenib is unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG believes that the comparison requested at the clarification stage should be explored by the company. However, it is unlikely that reliable data are available to inform an indirect treatment comparison (ITC).

1.4 The clinical effectiveness evidence: Summary of the ERG's key issues

The CS presents data from the INVICTUS randomised controlled trial (RCT) of ripretinib 150mg QD (once a day) plus BSC versus placebo plus BSC in 129 patients with advanced GIST who had progressed on, or were intolerant to, (at least) imatinib, sunitinib and regorafenib. Upon progression, patients randomised to ripretinib could discontinue ripretinib, continue their current dose of 150mg QD, or double their dose to 150mg twice a day (BID), whilst patients randomised to placebo who progressed could discontinue the study or switch to ripretinib 150mg QD. At the May 2019 cut-off, median PFS was 6.3 months for ripretinib versus 1.0 months for placebo (hazard ratio [HR] 0.15, 95% confidence interval [CI] 0.09 to 0.25, $p<0.0001$). Median OS was 15.1 months for ripretinib versus 6.6 months for

placebo (HR 0.36, 95% CI 0.21 to 0.62, *p*=not reported [NR]), 11.6 months in placebo crossover patients, and 1.8 months in placebo non-crossover patients. The most common treatment-emergent adverse events (TEAEs) with ripretinib (vs. placebo) were alopecia (52% vs. 5%); fatigue (42% vs. 23%); nausea (39% vs. 12%); abdominal pain (37% vs. 30%); constipation (34% vs. 19%); myalgia (32% vs. 12%); diarrhoea (28% vs. 14%); decreased appetite (27% vs. 21%); palmar-plantar erythrodysaesthesia syndrome (PPES) (21% vs. 0%) and vomiting (21% vs. 7%). TEAEs of special interest included squamous cell carcinoma (SCC) of the skin (2 [2.4%] vs. 0%) and actinic keratosis (5 [5.9%] vs. 1 [2.3%]).

The ERG's clinical advisors considered INVICTUS to be broadly representative of UK clinical practice. However, there were some differences between INVICTUS and the company's proposed use of ripretinib. The company's positioning of ripretinib is at fourth-line, whilst more than one-third of patients in INVICTUS had more than three prior therapies (see Issue 2). In addition, the company states that they are seeking a positive NICE recommendation on the use of ripretinib up to the point of disease progression, whereas in INVICTUS patients could receive ripretinib beyond progression, and clinical advisors to the ERG stated they would want to be able to use ripretinib beyond progression (see Issues 3 and 4).

Issue 2: Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial

Report section	4.2.3 and 5.3.5 (critical appraisal point [3])
Description of issue and why the ERG has identified it as important	The CS states that the company intends to position ripretinib as fourth-line therapy (in patients who have received exactly three prior therapies, including imatinib, sunitinib and regorafenib). However, more than one-third of patients in INVICTUS had already received at least four prior lines of treatment at study entry. The company's economic model is informed by the intention-to-treat (ITT) population of the trial. As such, there is a mismatch between the company's intended positioning of ripretinib and the available clinical evidence. The ERG's clinical advisors commented that the number of prior treatments is likely to be prognostic of outcomes. It is unclear whether the outcomes seen in the fourth- and later-line population in INVICTUS would be seen in the fourth-line population in NHS practice.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	The impact of this mismatch on the clinical effectiveness and cost-effectiveness of ripretinib is unclear.
What additional evidence or analyses might help to resolve this key issue?	It would be possible to restrict the trial data used in the model to include only those patients who have received exactly three prior treatments. However, this would limit the sample size, particularly for the placebo group, and may introduce confounding. The Appraisal Committee may wish to consider this issue in a deliberative manner when interpreting the results of the INVICTUS trial and the company's economic model.

1.5 The cost-effectiveness evidence: Summary of the ERG's key issues

The company's economic model assesses the cost-effectiveness of ripretinib plus BSC versus BSC alone for the fourth- and subsequent-line treatment of patients with advanced GIST. The model adopts a partitioned survival approach which includes three health states: (i) progression-free; (ii) progressed disease and (iii) dead. The analysis adopts an NHS and Personal Social Services (PSS) perspective, including QALYs accrued by GIST patients; caregiver effects are not included. Clinical outcomes for both treatment groups are based on parametric survival models fitted to data on PFS and OS from INVICTUS, including adjustment of OS in the BSC group to account for treatment switching which occurred in the placebo arm of the trial. The company's base case analysis assumes that ripretinib would be discontinued at progression, but does not include any adjustment of OS in the ripretinib group to account for post-progression ripretinib use in the intervention arm of the trial. Health state utility values are based on Euroqol 5-Dimensions 5-Level (EQ-5D-5L) data from INVICTUS (mapped to the 3-level version) which were not adjusted for post-progression ripretinib use in either group. Resource use and cost parameters were taken from a clinical expert survey used in NICE TA488, standard costing sources and other literature.

A Patient Access Scheme (PAS) has been agreed for ripretinib; this takes the form of a simple price discount of [redacted] (PAS price = [redacted] for 30 days' supply). All results presented in this ERG report include this PAS. The probabilistic version of the company's model suggests that compared with BSC, ripretinib generates an additional [redacted] QALYs at an additional cost of [redacted]; the corresponding ICER is £49,610 per QALY gained. The deterministic version of the model suggests a slightly lower ICER of £49,441 per QALY gained.

Issue 3: Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced OS outcomes and implausible OS predictions given the company's stopping rule

Report section	5.3.5 (critical appraisal points [4] and [5])
Description of issue and why the ERG has identified it as important	Patients in both arms of INVICTUS could receive ripretinib after disease progression. At the May 2019 data cut-off, 29 of 44 (66%) placebo group patients had crossed over to ripretinib and 42 of 85 (49%) ripretinib group patients had moved to open-label ripretinib after progression. The number of patients receiving open-label ripretinib at the January 2021 cut-off is not reported in the CS. All economic analyses presented in the CS include a stopping rule whereby all patients discontinue treatment at disease progression. The company's base case model includes adjustment of the OS data in the placebo group using the two-stage estimation method, but does not include any adjustment of the OS data in the ripretinib group. The company's base case model therefore assumes that the continued use of ripretinib post-progression has had no impact on the resulting estimates of OS in the INVICTUS trial – in other words, the company's model assumes that the same outcomes observed in the trial could be achieved by simply using less of the drug. The CS presents a scenario analysis which includes two-stage adjustment of the OS data in both treatment groups; this scenario results in an ICER of £93,739 per QALY gained, which is substantially higher than the company's base case ICER.

	The company's base case model also assumes that relative treatment effects persist indefinitely - the HR for OS for ripretinib versus BSC remains less than 1.0 at all time points. The company's model predicts a mean PFS of [redacted] years and a mean OS of [redacted] years in the ripretinib group (mean time alive with progressed disease = [redacted] years). The ERG's clinical advisors did not consider the company's model predictions of OS to be plausible given the stopping rule. They commented that if ripretinib was discontinued at progression, they would expect OS to be around 6 months longer than PFS.
What alternative approach has the ERG suggested?	The ERG's clinical advisors commented that they believe that continuing treatment with ripretinib post-progression will impact on OS. This view is supported by the company's switching analysis which leads to shorter estimates of mean OS for ripretinib compared with the unadjusted analysis.
What is the expected effect on the cost-effectiveness estimates?	The ERG-corrected deterministic ICER for ripretinib versus BSC is estimated to be £44,677 per QALY gained. The inclusion of OS adjustment in both treatment groups, together with the use of the ERG's preferred generalised gamma model for OS, increases the ICER for ripretinib versus BSC to £124,504 per QALY gained. This is a key model driver.
What additional evidence or analyses might help to resolve this key issue?	None. The ERG believes that if the company intends to apply a stopping rule for ripretinib, it is necessary to adjust OS data in both treatment groups to account for the effect of post-progression ripretinib use in INVICTUS.

Issue 4: Proposed stopping rule is not in line with existing recommendations on the use of TKIs

Report section	3.2
Description of issue and why the ERG has identified it as important	The company's proposed stopping rule requires all patients to discontinue ripretinib at the point of disease progression. The ERG's clinical advisors commented that if ripretinib was recommended by NICE, they would want to be able to continue to offer treatment with ripretinib beyond disease progression if patients were still deriving clinical benefit from it (i.e., they would want to be able to use ripretinib at fourth-line in the same way that regorafenib is currently used at third-line). The ERG's clinical advisors commented that they believe that giving ripretinib post-progression would improve OS. As such, they were concerned that the company's stopping rule directly conflicts with recommendations made in the 2017 UK clinical practice guidelines and the 2010 National Comprehensive Cancer Network (NCCN) Task Force guidelines on the use of tyrosine kinase inhibitors (TKIs) in patients with advanced and progressed GIST. These guidelines recommend maintaining treatment with TKIs even in patients with progressed disease, and comment that discontinuing TKIs in patients whose disease has progressed may lead to accelerated tumour growth.
What alternative approach has the ERG suggested?	The ERG believes that the company's proposed stopping rule has probably been proposed with the intention of improving the cost-effectiveness of ripretinib. It may be valuable for the company to present an economic analysis excluding the stopping rule (i.e., permitting treatment beyond progression on ripretinib).
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of ripretinib excluding the stopping rule is unclear.
What additional evidence or analyses might help to resolve this key issue?	An economic analysis which excludes OS adjustment for continued post-progression ripretinib use but which accounts for drug acquisition costs based on models fitted to time to treatment discontinuation (TTD) data in INVICTUS may be informative.

Issue 5: Uncertainty surrounding the level of HRQoL experienced by patients after progression on fourth-line therapy

Report section	5.3.5 (critical appraisal point [6])
Description of issue and why the ERG has identified it as important	The company's model includes health utility values for the progression-free and progressed disease states of [redacted] and [redacted], respectively. These values are based on EQ-5D-5L data collected in INVICTUS (mapped to the 3L version), without adjustment for post-progression ripretinib use in either treatment group. The ERG has concerns that the utility value applied in the progressed disease state is unlikely to be representative of the level of HRQoL of patients who have progressed disease and are receiving BSC alone. The ERG's clinical advisors commented that when patients discontinue TKI treatment, HRQoL deteriorates rapidly, in particular, due to the greater impact of disease symptoms. This decline is not reflected in the unadjusted INVICTUS data.
What alternative approach has the ERG suggested?	The ERG believes that the utility value for patients with progressed disease derived from the GRID trial (utility value = 0.647) may be more appropriate than the estimate obtained from the unadjusted INVICTUS data.
What is the expected effect on the cost-effectiveness estimates?	The ERG-corrected version of the company's model leads to an estimated ICER of £44,677 per QALY gained. Applying the utility value for patients with progressed disease from the GRID trial increases the ICER to £50,818 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input may be helpful in assessing the face validity of the utility values from the INVICTUS and GRID trials.

1.6 Summary of ERG's preferred model and sensitivity analysis results

The results of the ERG's preferred model and additional sensitivity analyses are summarised in Table 2. Exploratory analysis 1 (EA1) reflects the ERG-corrected version of the company's model (deterministic). EA2-5 also include these corrections. EA5 is the ERG's preferred model.

The company's original base case model suggests that the deterministic ICER for ripretinib versus BSC is £49,441 per QALY gained. The ERG's preferred model suggests a higher ICER of £134,241 per QALY gained. The main driver for this higher ICER is the inclusion of OS adjustment for continued post-progression ripretinib use in the ripretinib group of INVICTUS and the selection of the generalised gamma model fitted to the adjusted OS data. The ERG's additional sensitivity analyses suggest that the ICER is sensitive to the choice of OS model, but is less sensitive to the choice of PFS model and wastage assumptions.

Table 2: Summary of ERG's preferred model

Scenario	Incremental QALYs	Incremental costs	ICER	Change from company's base case
Company's base case	[redacted]	[redacted]	**£49,441**	**-**
ERG preferred analyses				
EA1: Correction of errors	[redacted]	[redacted]	£44,677	- £4,764
EA2: Inclusion of OS adjustment in ripretinib group and use of generalised gamma OS model	[redacted]	[redacted]	£124,504	+ £75,063
EA3: Utility value for progressed disease state based on GRID trial plus age-adjusted utility values	[redacted]	[redacted]	£50,818	+ £1,377
EA4: Inclusion of drug wastage assumptions	[redacted]	[redacted]	£45,747	- £3,694
EA5: ERG preferred analysis (deterministic)	[redacted]	[redacted]	**£134,241**	+ £84,800
Additional sensitivity analyses				
ASA1a: PFS = exponential	[redacted]	[redacted]	£128,872	+ £79,431
ASA1b: PFS = Weibull	[redacted]	[redacted]	£127,363	+ £77,922
ASA1c: PFS = Gompertz	[redacted]	[redacted]	£128,568	+ £79,127
ASA1d: PFS = log-normal	[redacted]	[redacted]	£134,241	+ £84,800
ASA1e: PFS = log-logistic	[redacted]	[redacted]	£137,665	+ £88,224
ASA1f: PFS = generalised gamma	[redacted]	[redacted]	£131,244	+ £81,803
ASA2a: OS = exponential	[redacted]	[redacted]	£115,722	+ £66,281
ASA2b: OS = Weibull	[redacted]	[redacted]	£137,032	+ £87,591
ASA2c: OS = Gompertz	[redacted]	[redacted]	£144,316	+ £94,875
ASA2d: OS = log-normal	[redacted]	[redacted]	£96,316	+ £46,875
ASA2e: OS = log-logistic	[redacted]	[redacted]	£100,315	+ £50,874
ASA2f: OS = generalised gamma	[redacted]	[redacted]	£134,241	+ £84,800
ASA3: Wastage = 0.5 packs	[redacted]	[redacted]	£137,633	+ £88,192

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ERG - Evidence Review Group; EA - exploratory analysis; ASA - additional sensitivity analysis; PFS - progression-free survival; OS - overall survival

Modelling errors identified by the ERG are described in Section 5.3.5. For further details of the exploratory and sensitivity analyses undertaken by the ERG, see Section 5.3.4.

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease (Section 2.1) and the company's overview of current treatment and their intended positioning of ripretinib (Section 2.2).

2.1 Company's description of the underlying health problem

2.1.1 Overview of GIST

The company's description of the disease (Section B.1.3 of the company submission [CS][1]) is summarised briefly here. The CS states that soft tissue sarcomas account for 1% of malignancies in adults, and gastrointestinal stromal tumours (GISTs) account for approximately 7% of all soft tissue sarcomas. GIST is a mesenchymal tumour of the gastrointestinal (GI) tract. GIST most frequently develops in the stomach (60-70% of cases) or small intestine (25-35% of cases), or in the colon, rectum or other rare sites (4-5% of cases). The median age at presentation is around 62 years, and GIST is not common in persons aged under 40 years (<10%).

The CS[1] states that the majority of patients present with symptoms at diagnosis and approximately half have acute or chronic GI bleeding. Symptoms are often non-specific and include GI pain, nausea, early satiety, abdominal bloating, anaemia, detection of an abdominal mass, gastric discomfort or ulcer-like symptoms. Common sites of GIST metastases include the liver (65%) and the peritoneum (21%), whilst less than 10% of tumours metastasise to the lungs or bones. Disease progression to advanced stages often leads to a negative impact on health-related quality of life (HRQoL) as well as a reduction in cognitive and social functioning. Patients with advanced GIST are also functionally impaired, with 19% having a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or 3. Section B.1.3 of the CS does not discuss expected survival of patients with advanced GIST after three prior therapies; the clinical advisors to the Evidence Review Group (ERG) commented that prognosis for these patients is very poor, with few patients receiving best supportive care (BSC) alone remaining alive after 12 months.

2.1.2 Genetics of GIST

The CS[1] (Section B.1.3.1) states that GIST is generally driven by mutations in the KIT (also referred to as CD117) or platelet derived growth factor receptor alpha (PDGFRA) receptor tyrosine kinases. These mutations often lead to constitutively activated KIT or PDGFRA (i.e., their cellular signalling activity is permanently "turned on"). Approximately 80% of GISTs have primary mutations in KIT, and 5-10% have a mutation in PDGFRA. Around 10% of GISTs lack mutations in KIT or PDGFRA genes and are referred to as wild-type; these cases often have mutations in other genes. Most primary KIT mutations involve a single mutation at diagnosis; however, secondary acquired mutations can also occur over time

in response to treatment with targeted tyrosine kinase inhibitor (TKI) therapies, leading to treatment resistance. Primary and secondary mutations are a known issue in GIST, and patients may have multiple mutations.

The ERG's clinical advisors agree that the company's description of GIST is broadly accurate.

2.2 Company's overview of current service provision

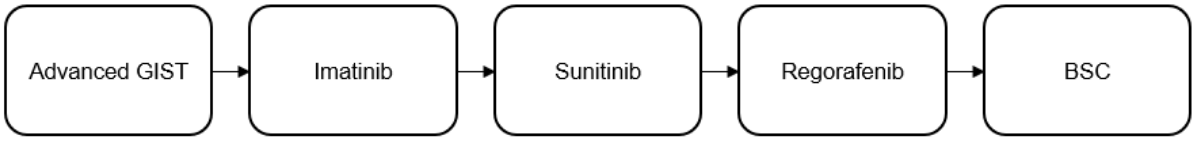
2.2.1 Primary localised GIST: surgery and adjuvant imatinib

The CS[1] (Section B.1.3.3) states that surgery is the recommended approach for primary and localised GIST and is the only potentially curative option. The CS also states that a third of patients have an intermediate to high risk of disease progression and approximately 50% have disease recurrence within 2 to 3 years following resection. Patients at high risk of recurrence can receive adjuvant imatinib for up to 3 years.

2.2.2 Current clinical management of advanced GIST

The company's view of the current treatment pathway for advanced GIST is shown in Figure 1. Whilst not shown in the diagram, all TKIs would be given alongside BSC. The CS[1] (Section B.1.3.3) states that approximately 50% of patients present with metastatic or unresectable GIST at diagnosis and around 40-90% of surgical patients develop subsequent recurrence or metastasis. Targeted therapy with TKIs is the standard of care for metastatic or unresectable GIST due to their anti-KIT and anti-PDGFRA properties. Imatinib is the standard first-line treatment in England. Disease progression after imatinib treatment occurs mostly due to primary resistance, secondary KIT mutation or inadequate drug exposure. If progression or imatinib intolerance is confirmed, the standard second-line treatment is sunitinib. Most patients will again relapse within 6 months to 1 year due to additional or alternative secondary mutations in KIT, or due to multiple different KIT mutations occurring in different areas of the tumour. In addition, some imatinib-resistant patients have primary resistance to sunitinib due to the specific secondary mutation(s) that arise during imatinib treatment. Regorafenib is regarded as standard therapy for the third-line treatment of patients progressing on or failing to respond to imatinib and sunitinib.

Figure 1: Current treatment pathway for advanced GIST (reproduced from CS, Figure 3)

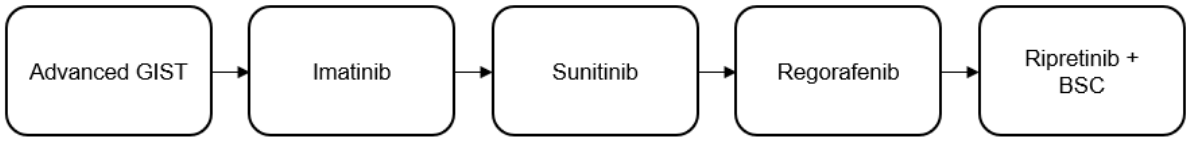


BSC - best supportive care; GIST - gastrointestinal stromal tumour

2.2.3 Company's positioning of ripretinib in the treatment pathway

The CS[1] (Section B.1.3.3) states that there are currently no further treatment options for GIST patients in the UK who have received prior treatment with three or more kinase inhibitors including imatinib, other than BSC. The CS states that the proposed place of ripretinib (a novel TKI) is in the fourth-line treatment of GIST, as shown in Figure 2. The ERG notes that whilst not shown in Figure 2, subsequent treatment after ripretinib would be BSC alone. In addition, whilst not explicitly stated in the CS,[1] the company's clarification response[2] (question A2) states that the company is seeking a positive recommendation from the National Institute for Health and Care Excellence (NICE) for ripretinib only up to the point of disease progression.

Figure 2: Proposed position of ripretinib in the pathway for advanced GIST (reproduced from CS, Figure 4)



BSC - best supportive care; GIST - gastrointestinal stromal tumour.

2.2.4 ERG's critique of the company's treatment pathway and positioning of ripretinib

The ERG's clinical advisors agree that the company's description of the treatment pathway is accurate. The company's positioning of ripretinib within the pathway is broadly consistent with the final NICE scope[3] and the marketing authorisation for ripretinib.[4] However, the ERG notes that the company's target population relates specifically to people who have received three prior therapies, i.e., the use of ripretinib at fourth-line, whereas more than one-third of patients in the INVICTUS trial[5] (the pivotal trial of ripretinib for GIST for this appraisal) had received more than three prior therapies. The ERG's clinical advisors also commented that many patients who progress on third-line regorafenib will continue to receive this treatment after disease progression if they are still deriving clinical benefit from it and there are no other alternative treatment options, whilst the remainder will receive BSC alone; this has implications for the relevant comparators for ripretinib. The clinical advisors further stated that they would want to be able to use ripretinib in the same way that regorafenib is used, i.e., including the option to continue to offer treatment with ripretinib beyond progression in patients who are still obtaining clinical benefit from it. These issues are discussed further in Sections 3.1 to 3.3.

3. CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[3] and addressed in the CS is presented in Table 3. The ERG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: The decision problem (reproduced from CS Table 1, with minor amendments and comments from the ERG)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from final NICE scope	ERG comments
Population	Adults with advanced GIST who have had at least 3 prior therapies, or have documented intolerance to any of these treatments	Adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib	As marketing authorisation in SmPC[4] – see appendix C	The company's intended positioning of ripretinib is specifically as fourth-line therapy (see CS,[1] Section B.1.3.3, page 21). Patients in INVICTUS[5] had received between 3 and 7 prior therapies at baseline.
Intervention	Ripretinib	As per scope	N/a	Patients in INVICTUS[5] were permitted to continue treatment with ripretinib beyond disease progression. The marketing authorisation for ripretinib[4] permits continued treatment beyond disease progression. However, the company's clarification response[2] (question A2) states that *"The company are seeking reimbursement for the use of ripretinib only up to the point of disease progression."* The company's economic model assumes that all patients will discontinue treatment at the point of disease progression. The ERG's clinical advisors stated that they would want to use ripretinib beyond disease progression in patients who are still obtaining clinical benefit from treatment.
Comparator(s)	Established clinical management without ripretinib including BSC	As per scope	N/a	The ERG's clinical advisors commented that in usual practice many patients will receive regorafenib beyond progression rather than BSC.
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate (including partial response rate and duration of response) • Adverse effects of treatment • HRQoL	As per scope	N/a	The CS[1] reports outcomes data from INVICTUS[5] for all endpoints listed in the NICE scope.[3] The company's model uses data from INVICTUS on OS, PFS, AEs and HRQoL.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from final NICE scope	ERG comments
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per scope. The ripretinib marketing authorisation is independent of mutational status, According to UK clinical practice, all GIST patients are routinely tested for mutations on diagnosis.[6, 7] Therefore, no additional diagnostic testing is expected.	N/a	The company's model estimates the incremental cost per QALY gained for ripretinib (plus BSC) versus BSC in adult patients with advanced GIST after three prior therapies.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Previous treatment with TKIs whose disease has progressed • Resistance or intolerance to TKIs	No subgroups considered	All patients of interest are resistant or intolerant or have progressed on tyrosine kinase inhibitors	No economic subgroup analyses are presented in the CS.[1]
Special considerations including issues related to equity or equality	None identified.	There are no special considerations relating to issues of equity or equality.	N/a	The CS[1] argues that ripretinib meets NICE's End of Life criteria.

NICE - National Institute for Health and Care Excellence; CS - company's submission; ERG - Evidence Review Group; GIST - gastrointestinal tumour; SmPC - Summary of Product Characteristics; BSC - best supportive care; OS - overall survival; PFS - progression-free survival; AE - adverse event; HRQoL - health-related quality of life; QALY - quality-adjusted life year; TKI - tyrosine kinase inhibitor; N/a - not applicable

3.1 Population

The final NICE scope[3] specifies the relevant population as adults with advanced GIST who have had at least three prior therapies, or have documented intolerance to any of these treatments. The main clinical evidence for ripretinib included in the CS[1] comes from the INVICTUS randomised controlled trial (RCT).[5] Patients enrolled in INVICTUS were adults with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications. The European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for ripretinib relates to *"adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib."*[4] As such, the populations defined in the NICE scope, the key clinical evidence and the marketing authorisations are all broadly aligned.

The ERG notes that the company's target population relates specifically to people who have received three prior therapies, including imatinib, sunitinib, and regorafenib. Section B.1.3.3 of the CS[1] (page 21) states that *"It is therefore proposed that the place of ripretinib would be in the fourth-line of treatment, alongside BSC."* However, more than one-third of the patient population in the INVICTUS trial[5] had received more than three prior therapies. As such, the company's intended positioning of ripretinib as a fourth-line therapy means that the target population is a subgroup of the overall population covered by the EMA/MHRA licence and the clinical evidence from INVICTUS. However, the clinical evidence presented in the CS and the company's economic model both reflect outcomes data for the whole intention-to-treat (ITT) population of INVICTUS, which includes patients who have received three or more prior therapies.

3.2 Intervention

The intervention described in the CS[1] is consistent with the final NICE scope.[3] The intervention under consideration is ripretinib (Qinlock®). Ripretinib is a novel TKI that inhibits KIT proto-oncogene receptor tyrosine kinase and PDGFRA kinase, including wild-type, primary, and secondary mutations. Ripretinib also inhibits other kinases *in vitro*, such as PDGFRB, TIE2, VEGFR2, and BRAF.[4]

A full marketing authorisation for ripretinib was issued by the MHRA in December 2021. According to the Summary of Product Characteristics (SmPC) for ripretinib,[4] the recommended dose is 150mg ripretinib (three 50mg tablets) taken once daily at the same time each day with or without food. Ripretinib is administered orally in tablet form. The list price per pack of 90 x 50mg ripretinib tablets (30 days' supply) is £18,400. After the CS[1] was received by the ERG, a Patient Access Scheme (PAS) was agreed for ripretinib: this takes the form of a simple price discount of [redacted]. The price per pack of ripretinib including the PAS is [redacted].

The CS[1] states that no additional testing is required for treatment with ripretinib (see Table 3). The ERG's clinical advisors agree with this.

The INVICTUS trial[5] allowed patients in the ripretinib group to continue to receive the study drug after disease progression. The SmPC for ripretinib[4] states that treatment with ripretinib should continue as long as benefit is observed or until unacceptable toxicity; as such, treatment beyond disease progression is permitted under the licence. However, the company's clarification response[2] (question A2) states that *"The company are seeking reimbursement for the use of ripretinib only up to the point of disease progression."* The company's base case economic model assumes that treatment with ripretinib would be discontinued for all patients at the point of disease progression. Potential confounding of overall survival (OS) data resulting from the use of ripretinib after disease progression is not adjusted for in the company's base case analysis, but is considered in one scenario analysis (see Section 5.2.6). The ERG's clinical advisors commented that, if ripretinib was recommended by NICE, they would want to be able to continue to offer treatment with ripretinib beyond disease progression if patients were still deriving clinical benefit from it, and they expected their views on this issue to be representative of the broader clinical community. The clinical expert consulted by the company also suggested that they would consider the use of continued post-progression ripretinib for heavily pre-treated GIST patients if radiological progression is limited, if the patient is tolerating the therapy and if no other treatments are available (see clarification response,[2] question A2). The ERG's clinical advisors also commented that they expected continued ripretinib given after disease progression to improve OS and they were particularly concerned that the company's proposed stopping rule runs contrary to clinical recommendations on the use of TKIs in patients with advanced and progressed GIST:

"In the setting of active disease progression on TKI therapy, discontinuing therapy may lead to accelerated tumor growth by withdrawing control of sensitive clones of the disease (even if limited disease sites have been shown to exhibit resistance to therapy and hence to progress more rapidly). Therefore, in the absence of a clinical trial testing a different hypothesis, the task force panel strongly feels that continuing TKI therapy should be an essential component of best supportive care for patients with progressive disease." (National Comprehensive Cancer Network [NCCN] Task Force, 2010).[8]

"…there is anecdotal evidence that maintaining treatment with a TKI even in the case of progressive disease, as opposed to stopping it, may slow down progression if no other option is available at the time. Therefore, re-challenging or continuing treatment with a TKI, to which the patient has already been exposed, is an option which may be considered for symptom control in patients with progression." (UK GIST clinical practice guidelines, 2017).[6]

3.3 Comparators

The final NICE scope[3] lists a single comparator: *"Established clinical management without ripretinib including BSC."* The INVICTUS trial[5] was placebo-controlled, and the comparator considered in the CS[1] and the company's economic model is BSC alone. Patients who were randomised to the placebo group of INVICTUS were permitted to switch treatment to receive ripretinib after disease progression; the company's economic model includes statistical adjustment of the OS data to account for potential confounding caused by treatment switching onto ripretinib in the placebo arm of the trial.

The ERG's clinical advisors commented that many patients who progress on regorafenib will continue to receive this treatment beyond disease progression if they are still deriving clinical benefit from treatment, whilst the remainder will receive BSC alone. The clinical advisors commented that stopping regorafenib after progressing on third-line treatment leads to an acceleration of further tumour progression. They also commented that treatment with regorafenib in patients with progressed disease would continue for as long as the patient is able to continue taking this medication.

The company's clarification response[2] (question A3) agrees that some patients continue to receive regorafenib beyond disease progression. However, the company's response (question C5) argues that post-progression regorafenib is not a relevant comparator for this appraisal and suggests that a positive NICE recommendation for ripretinib would not alter the current use of post-progression regorafenib. The ERG's clinical advisors disagreed with the company's view: instead, they suggested that if ripretinib received a positive recommendation from NICE, patients would be switched onto ripretinib as soon as they have progressed on regorafenib. This suggests that post-progression regorafenib should be considered a relevant comparator for ripretinib. However, no clinical evidence or economic analyses have been provided by the company to inform this comparison.

3.4 Outcomes

The following outcomes are listed in the final NICE scope:[3]

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rate (including partial response rate and duration of response)
- Adverse effects of treatment
- HRQoL.

The CS[1] reports on all of these outcomes for the ITT population of INVICTUS.[5] The company's economic model is informed by data on PFS, OS, adverse events (AEs) and HRQoL from INVICTUS (see Section 5.2).

3.5 Other relevant factors

Section B.1.4 of the CS[1] states that there are no known equality issues relating to the use of ripretinib for treating advanced GIST after three therapies.

The CS[1] argues that ripretinib meets NICE's End of Life (EoL) criteria. The evidence to support this argument is summarised and critiqued in Chapter 6.

4. CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[1] is comprised of:

- A systematic literature review (SLR)
- Summary and results for the INVICTUS[5] trial of ripretinib.

This chapter summarises and critiques the company's review methods and clinical effectiveness data. Full details are presented in the CS[1] Section B.2 and the CS Appendices D, E and F.[9]

4.1 Critique of the methods of review

4.1.1 Searches

The company performed an initial SLR in July 2020 followed by two updates in July 2021 and March 2022. The SLR aimed to identify all clinical effectiveness and safety studies of ripretinib or comparator treatments of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors.

In summary, the ERG has identified several limitations in the company's clinical effectiveness searches:

- Search limited by prior treatment (fourth- and subsequent-line studies)
- Lack of intervention and comparator terms
- Restricted field searching
- Statement combination error.

The company searched several electronic bibliographic databases in March 2022 (CS Appendix D[9]): MEDLINE; MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations; EMBASE and Cochrane Library. All database searches were undertaken simultaneously by the company in a single platform (Ovid). The ERG only has access to MEDLINE and Embase in the Ovid host platform.

The company searched several key conference abstract websites for up to five years: the American Society of Clinical Oncology (ASCO, 2018-2021); the European Society of Medical Oncology (ESMO, 2017-22) and the ASCO Gastrointestinal Cancers Symposium (ASCO GI, 2018-2021).

The company only searched the clinicaltrials.gov registry for ongoing or completed or unpublished trials; two further trials registries could have been searched – the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (EUCTR). The company also searched the websites of four health technology assessment (HTA) agency in August 2021: NICE; the Scottish Medicines Consortium (SMC); the Pharmaceutical Benefits Advisory Committee (PBAC) and the Canadian Agency for Drugs and Technologies in Health (CADTH). The reported searches in the CS[1] are transparent and fully reported.

The company conducted an all-in-one database search within the Ovid host platform. The controlled vocabulary/index terms in MEDLINE and Embase differ (Embase has more indexing terms attached to records compared to MEDLINE) and the company was aware of the necessity to include both MeSH and Emtree terminology in the search strategy. The company applied multiple concept combinations to the search for the population (disease GIST AND "metastatic/advanced/unresectable" AND relapsed/refractory/resistant). The terms applied were comprehensive and the ERG does not consider that these combinations were restrictive, having explored the effects of removing one of the concepts (relapsed/refractory/resistant) in the MEDLINE and Embase search (in Ovid) on the number of records retrieved and screened to see if relevant studies were missed.

The company's searches limited the population to patients who have had prior treatment (imatinib, sunitinib and regorafenib). The ERG questions the appropriateness of applying this concept to the search since all patients who receive the intervention and comparator treatments will have received these treatments as first-, second- and third-line. Also, there are two major limitations to this search approach: (i) the company did not include the synonyms/drug trade names in the search, and (ii) the company should have used the "multi-purpose" field searching (which will include trade names, registry numbers and chemical names of the drugs) rather than a title and abstract search to mitigate the limitation of not including all of the drug synonyms in the search. The ERG considers that applying the prior therapy concept to the search may have had a negative impact on the sensitivity and recall of the search for the studies of the intervention and comparators. Instead, the ERG would recommend including the terms and searching for the intervention (ripretinib) and other comparators studied for fourth-line GIST as the terms for the prior treatment may not necessarily be mentioned in the title and abstracts of potentially relevant studies of ripretinib or the other comparators. There was a notable Boolean logic error in the search terms presented in Table 2 of CS Appendix D.5.6,[9] whereby statement 11, which should have been "or/8-10", is missing; therefore, statement 12 of the search is incorrect. If uncorrected, the impact of this would be consequential.

The ERG has attempted to replicate the company's MEDLINE and Embase searches (via Ovid) with and without applying the prior treatment concept, and concluded that the inclusion of this concept would result in missed studies of the intervention and comparators. Whilst there is only one relevant trial in the CS[1] (the INVICTUS RCT[5]), the ERG is not aware of any relevant studies reported in the CS that have been missed. However, given the limitations of the clinical effectiveness search, it is unclear to the ERG how and where all the included studies have been identified from the searches. It is possible that relevant studies may have been identified through the other searches reported in the CS or via the Cochrane Library search.

4.1.2 Inclusion criteria for the SLR

The clinical SLR described in the CS[1] is broader than the decision problem. The SLR included RCTs and single-arm interventional studies of patients with advanced GIST receiving fourth- and subsequent-line therapy, published from the year 2000 onwards. The included interventions were: ripretinib; imatinib; regorafenib; sunitinib; BSC and other interventions for fourth- and subsequent-line GIST. The ERG considers the inclusion criteria to be appropriate to identify RCTs of ripretinib for fourth- and subsequent-line GIST.

4.1.3 Critique of study selection, data extraction and quality assessment

Two reviewers screened all citations and full-text articles (CS Appendix D.6.2[9]). Extracted data were checked by a second reviewer. Study quality for the included RCT was assessed using the NICE quality assessment checklist (CS Appendix D.8[9]). The ERG considers these methods to be appropriate.

4.1.4 Overall ERG view on company's review methods

Overall, the ERG considers that the majority of the company's review methods were appropriate, other than the limitations in the search described in Section 4.1.1.

4.1.5 Results of the company's SLR

The company's clinical SLR identified 25 publications, 11 of which assessed ripretinib and so were relevant to this submission (CS,[1] Section B.2.2). Of these, 9 publications related to the INVICTUS trial of ripretinib, the primary references being the INVICTUS Clinical Study Report (CSR)[5] and Blay *et al.* (2020).[10] A further two publications[11, 12] related to a Phase 1 non-randomised dose-escalation study of ripretinib; these publications are not discussed further in the CS or the ERG report. Therefore, the SLR identified only one relevant study: the INVICTUS RCT of ripretinib.

4.2 Characteristics of INVICTUS study of ripretinib

4.2.1 Study design: INVICTUS

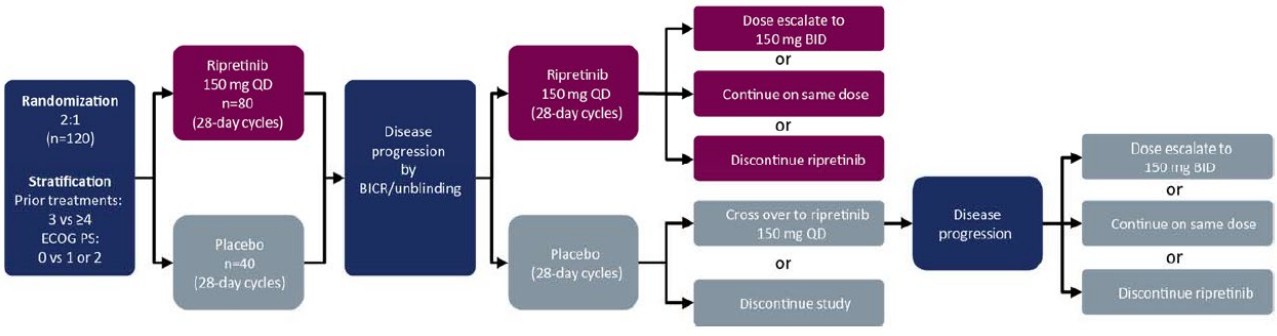
The company's SLR identified one relevant RCT of ripretinib. INVICTUS[5] is an international, multicentre, randomised, double-blind, placebo-controlled Phase 3 trial in patients with advanced GIST after at least 3 prior anticancer therapies, comparing the efficacy of ripretinib plus BSC versus placebo plus BSC (CS[1] Section B.2.3). The study was conducted at 29 specialised hospitals across 12 countries across North America, Europe, and Asia. The design of the INVICTUS RCT is summarised in Table 4 and Figure 3.

Table 4: Design of INVICTUS study (adapted from CS, Table 6 and Table 9)

Study	INVICTUS (NCT03353753)
Study design	Phase 3, multicentre, double-blind, placebo-controlled, randomised trial
Settings and locations	North America, Europe, and Asia (29 specialised hospitals)
Population	• Patients with GIST aged ≥18 years • ECOG PS of 0-2 • Disease progression on (at least) imatinib, sunitinib and regorafenib, or documented intolerance to any of these (i.e., fourth-line or later)
Randomisation stratified by	• 3 versus ≥4 prior anticancer treatments • ECOG PS of 0 versus 1 or 2
Intervention(s)	Ripretinib 150mg QD + BSC (n=85)
Comparator(s)	Placebo + BSC (n=44)
Duration of treatment and options after disease progression	• Ripretinib: 150mg QD until disease progression or unacceptable toxicity. Upon progression, patients randomised to ripretinib could discontinue ripretinib, continue their current dose of 150mg per day, or double their dose to 150mg BID • Placebo: Upon progression, patients randomised to placebo could discontinue the study or cross over to ripretinib 150mg QD
Reported outcomes specified in the decision problem	• PFS • OS • Response rates • AEs • HRQoL: EQ-5D-5L, EQ-VAS, EORTC QLQ-C30 (physical and role functioning domains only)
All other reported outcomes	TTP

AE - adverse event; QD - once a day; BID - twice a day; BSC - best supportive care; ECOG - Eastern Cooperative Oncology Group; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-5D-5L - EuroQol 5 dimensions (5-level); EQ-VAS - EuroQol visual analogue scale; GIST - gastrointestinal stromal tumour; HRQoL - health-related quality of life; OS - overall survival; PFS - progression-free survival; PS - performance status; TTP - time to progression

Figure 3: INVICTUS study design and treatment allocation (reproduced from CS, Figure 5)



BID - twice a day; BICR - blinded independent central review; ECOG - Eastern Cooperative Oncology Group; PS - performance status; QD - once a day
Note: Randomisation was stratified based on prior lines of therapy (3 vs ≥4) and ECOG (0 vs 1 or 2)
Source: Blay et al. 2020,[10] supplementary appendix, Figure S1.

Population in INVICTUS

The INVICTUS trial[5] included 129 patients with advanced GIST who had received at least three prior anticancer therapies including (at least) imatinib, sunitinib and regorafenib. The inclusion criteria for INVICTUS are slightly more restrictive than the final NICE scope[3] (which specifies at least three prior therapies) and the SmPC for ripretinib[4] (which specifies at least three prior kinase inhibitors including imatinib). However, the ERG's clinical advisors considered that the inclusion criteria reflect the characteristics of patients with advanced GIST in England who would be eligible for ripretinib as fourth- or subsequent-line therapy. The ERG notes that approximately one-third of patients in INVICTUS received more than 3 prior therapies (so were at fifth-line or later), whilst the company's intended positioning for ripretinib is specifically as fourth-line therapy. A total of 10 patients (8%) in INVICTUS were from the UK (see clarification response,[2] question A3).

Intervention in INVICTUS

Patients were randomised 2:1 to ripretinib plus BSC versus placebo plus BSC. In total, 85 patients were randomised to ripretinib and 44 to placebo. The ripretinib dose was 150mg QD (once a day) until disease progression or unacceptable toxicity.

Upon progression, patients and investigators were unblinded, and patients randomised to ripretinib could either discontinue ripretinib, continue their current dose of 150mg QD, or double their dose to 150mg BID (twice per day). Patients randomised to placebo could discontinue the study or cross over to receive ripretinib 150mg QD. The company's clarification response[2] (question A4) states that the rationale for permitting patients in the ripretinib group to double their dose was because this higher dose was well-tolerated in the Phase 1 study (NCT02571036) and so was offered to patients with disease progression in INVICTUS[5] due to the lack of alternative treatments, even though 150mg QD was established as the recommended dose based on safety, pharmacokinetics, and pharmacodynamics data. The ERG notes that the recommended dose in the SmPC for ripretinib[4] is 150mg QD, and the company's clarification response[2] states that reimbursement is not being sought for the 150mg BID dose.

In contrast to the experience of the INVICTUS trial,[5] the company's clarification response[2] (question A2) states that the company is seeking a positive NICE recommendation for the use of ripretinib only up to the point of disease progression. The company's response also states that a UK clinician advised the company that treatment would generally be stopped at clear/aggressive progression, but may be continued if radiological progression is limited, if the patient continues to have clinical benefit, and if no alternative treatment option is available. As discussed in Section 3.2, the ERG's clinical advisors commented that they would want to be able to offer continued treatment with ripretinib beyond disease progression if the patient was experiencing clinical benefit, as currently occurs with third-line regorafenib.

Comparator in INVICTUS

The comparator in INVICTUS[5] was placebo plus BSC. The ERG's clinical advisors considered that it was reasonable to compare against placebo plus BSC, since there are no further recommended therapies at fourth-line (or subsequent-line) in England. However, as noted in Section 3.3, the ERG's clinical advisors commented that many patients currently continue regorafenib after progression if they are experiencing clinical benefit. Continued post-progression regorafenib was not a comparator in the INVICTUS trial and the CS[1] does not provide an indirect treatment comparison (ITC) between fourth-line ripretinib and continued regorafenib post-progression.

Outcomes in INVICTUS

Outcomes included PFS, OS, time to progression (TTP), response rates, AEs, and HRQoL, based on the 5-level EuroQol 5 dimensions (EQ-5D-5L) questionnaire, the EuroQol visual analogue scale (EQ-VAS) and the physical and role functioning domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item questionnaire (EORTC QLQ-C30).

Study quality of INVICTUS

Quality assessment of INVICTUS[5] is presented in CS Appendix D.8.[9] The CS[1] reports the study to be of high methodological quality in terms of randomisation, baseline comparability of groups, blinding of patients and staff, no unexpected imbalances in drop-outs, no selective outcome reporting, and use of ITT analysis. The ERG largely agrees with the company's quality assessment.

However, the ERG notes the following points regarding study design:

a) There were some differences in baseline characteristics between groups (see Section 4.2.4)
b) The study was unblinded on progression, and patients were permitted to continue or change treatment on progression. These factors may have impacted on OS, which was measured until the patient died.

Analysis populations and data cut-offs in INVICTUS

The data cut-offs for INVICTUS[5] were as follows (CS,[1] Section B.2.3):

- Primary data cut-off: 31st May 2019 (Blay *et al.*, 2020)[10]
- Additional analysis with extra 9 months of follow-up: data cut-off 9th March 2020 (Zalcberg *et al.*, 2020 abstract)[13]
- Additional analysis with extra 19 months of follow-up: data cut-off 15th January 2021 (von Mehren *et al.*, 2021 abstract).[14]

The analysis populations were as follows:

- Primary efficacy analyses were based on the ITT population, defined as all randomised patients (n=129). The period analysed was the double-blind period for all outcomes except OS, which followed up patients until they died.
- Safety population, which included all randomised patients who received at least one dose of study drug (n=128).

4.2.2 Participant flow in INVICTUS

Participant flow for the May 2019 data cut-off is shown in Figure 4 and Table 5. In total, 129 patients were randomised: 85 to ripretinib and 44 to placebo (one placebo patient did not receive treatment). In the placebo group, 29 of 44 patients (66%) crossed over to ripretinib 150mg QD upon progression, whilst 15 of 44 patients (34%) did not cross over (CS,[1] Section B.2.6).

In the ripretinib group, at the May 2019 cut-off, 26 of 85 patients (31%) were still on double-blind ripretinib, 17 of 85 patients (20%) had discontinued double-blind treatment, and 42 of 85 patients (49%) had moved to open-label ripretinib after progression (the CS does not state how many received 150mg QD or 150mg BID), some of whom later discontinued. The proportions of patients still receiving ripretinib (either double-blind or open-label) at the May 2019 data cut-off were: 36 of 85 patients (42%) in the ripretinib group and 11 of 44 patients (25%) in the placebo group.

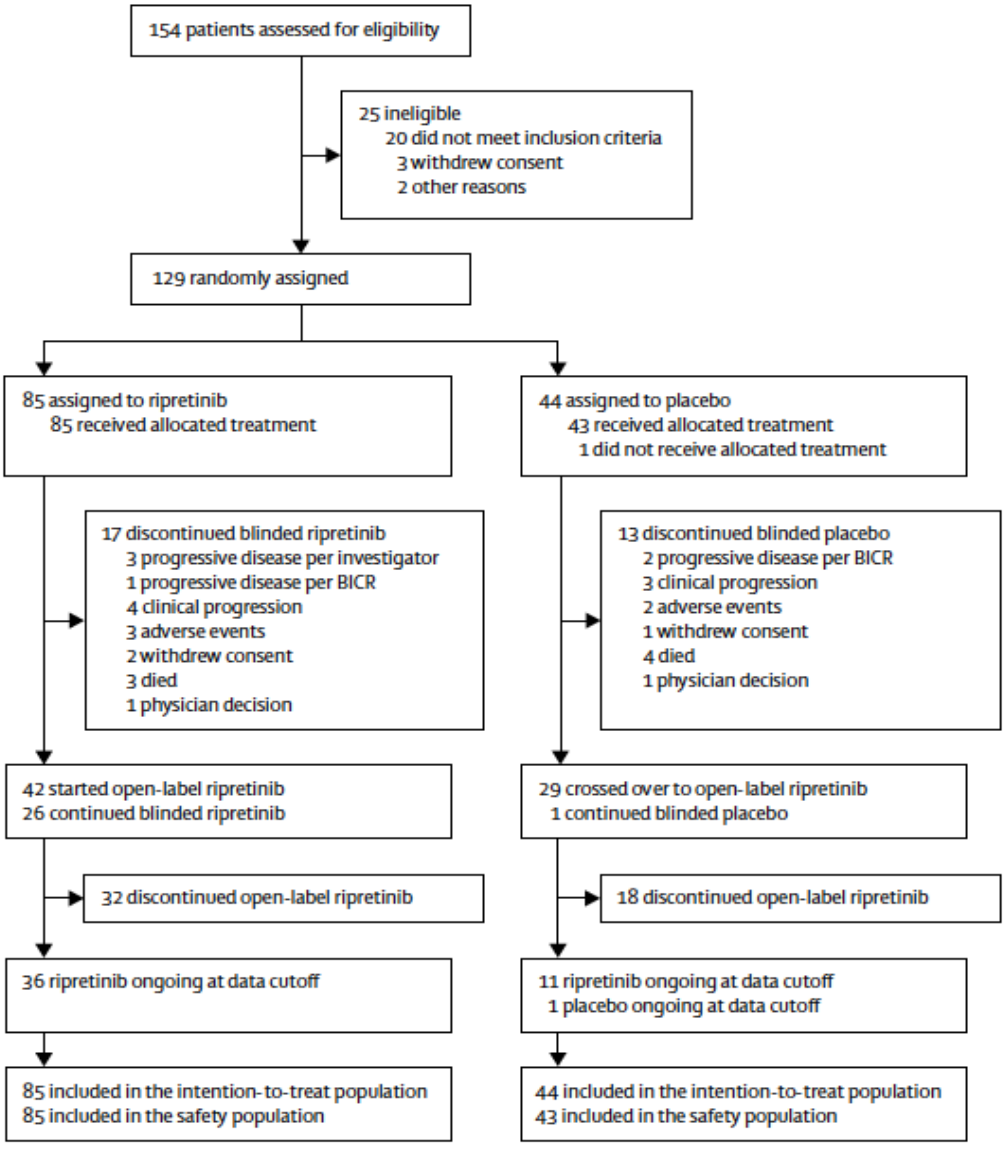
The company's clarification response[2] (question A5) provides data on patient flow for the cut-off of the 10th August 2020. At this point, 65 patients in the ripretinib group had progressed, of whom 43 dose-escalated to ripretinib 150mg BID and 22 either continued ripretinib 150mg QD or discontinued ripretinib (the CS[1] does not report how many of these patients continued or discontinued). The median duration of treatment with ripretinib 150mg BID was 3.7 months (range: 1 day to 18.6 months) and 11 of 43 patients (26%) received ripretinib 150mg BID for 6 months or longer. The number of patients receiving ripretinib 150mg QD post-progression, and the duration, was requested by the ERG but was not provided by the company.

Table 5: Flow of participants in INVICTUS and proportions still on treatment, May 2019

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

BID - twice a day; QD - once a day

Figure 4: Flow of participants in the INVICTUS trial, May 2019 (reproduced from CS Appendix D.7.2, Figure 3)



BICR - blinded independent central review
Data reported as of the cut-off date for the primary completion date (31st May, 2019)

4.2.3 Baseline characteristics in INVICTUS

Patient baseline characteristics in INVICTUS[5] are shown in Table 6. The ERG's clinical advisors considered that the patient characteristics in INVICTUS were generally representative of patients in clinical practice in England and were reasonably balanced between groups. The ERG notes that approximately one-third of patients in INVICTUS had received more than three prior therapies, whilst the company's intended positioning for ripretinib is as fourth-line therapy (see CS,[1] Section B.1.3.3, page 21). The ERG's clinical advisors noted that patients at later lines may have a worse prognosis due to pre-treatment and development of resistance mutations; conversely, patients who are still on treatment at later lines may have biologically less aggressive disease. Subgroup analyses of outcomes for INVICTUS are presented in Section 4.3 of this ERG report.

Patients in the ripretinib group were younger than in the placebo group (59 vs. 65 years) with fewer patients aged ≥75 years (9% vs. 23%). The ERG's clinical advisors noted that this may have had some limited impact on outcomes, favouring ripretinib (again, subgroup analyses are presented in Section 4.3 of this ERG report). The ripretinib group had slightly fewer male patients (55% vs. 59%). The ripretinib group had slightly more patients with more than three prior therapies (64% vs. 61%) and slightly more patients with ECOG PS 0 (44% vs. 39%). The ripretinib group had a slightly higher frequency of primary gastric tumours (47% vs 41%), a lower frequency of KIT exon 11 mutations (55% vs. 64%) and higher frequency of PDGFRA mutations (4% vs. 0%).

During the clarification round, the ERG requested data on the percentage of patients who had progressed on, were resistant to, or were intolerant to prior TKIs (see clarification response,[2] question A8). However, the company stated that these data were not available. The ERG's clinical advisors noted that patients who were resistant to or progressed on prior therapies may have a worse prognosis than those who switched treatment due to intolerance, and that patients with primary resistance may have a worse prognosis than those progressing later.

Table 6: Baseline characteristics in INVICTUS (adapted from CS, Table 8)

Characteristics	Ripretinib (n=85)	Placebo (n=44)
Age		
Median age, range (years)	59 (29–82)	65 (33–83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Female	38 (45%)	18 (41%)
Race		
White	64 (75%)	33 (75%)
Non-white	13 (15%)	7 (16%)
Not reported	8 (9%)	4 (9%)
Region		
USA	40 (47%)	20 (46%)
Non-USA	45 (53%)	24 (55%)
Number of previous therapies		
3	54 (64%)	27 (61%)
4–7	31 (36%)	17 (39%)
ECOG PS		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)
Primary tumour site		
Gastric	40 (47%)	18 (41%)
Jejunum or ileum	20 (24%)	8 (18%)
Mesenteric or omental	6 (7%)	6 (14%)
Other	7 (8%)	4 (9%)
Duodenum	2 (2%)	8 (18%)
Colon or rectum	9 (11%)	0
Unknown	1 (1%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123 (28–495)	142 (17–412)
Primary mutation (central testing of tumour tissue)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other *KIT*	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0
KIT and *PDGFRA* wild-type	7 (8%)	3 (7%)
Not available† or not done‡	12 (14%)	5 (11%)

ECOG - Eastern Cooperative Oncology Group; PS - performance status; ITT - intention-to-treat; PDGFRA - platelet-derived growth factor receptor α

** Independent assessment. † Tumour tissue analysed for baseline mutations but analysis failed. ‡ Biopsy completed per protocol but sample not received for analysis.*

Source: Blay et al. 2020,[10] Table 1

4.3 Effectiveness of ripretinib

Effectiveness data for ripretinib based on the INVICTUS trial[5] are summarised in this section. Full details are provided in Section B.2.6 of the CS[1] and CS Appendices D, E and F.[9]

4.3.1 Progression-free survival (PFS)

As shown in Table 7 and Figure 5, the median PFS in May 2019 was 6.3 months for ripretinib versus 1.0 months for placebo (hazard ratio [HR] 0.15, 95% confidence interval [CI] 0.09 to 0.25, $p<0.0001$). At later data cut-offs, PFS data were very similar (Table 7).

PFS2 for patients crossing over from placebo to ripretinib

In an exploratory analysis of PFS2 in the open-label period for the 29 (of 44) patients crossing over from placebo to ripretinib (Table 7), median PFS2 was 4.6 months (CS,[1] Section B.2.6).

PFS for patients dose escalating on progression

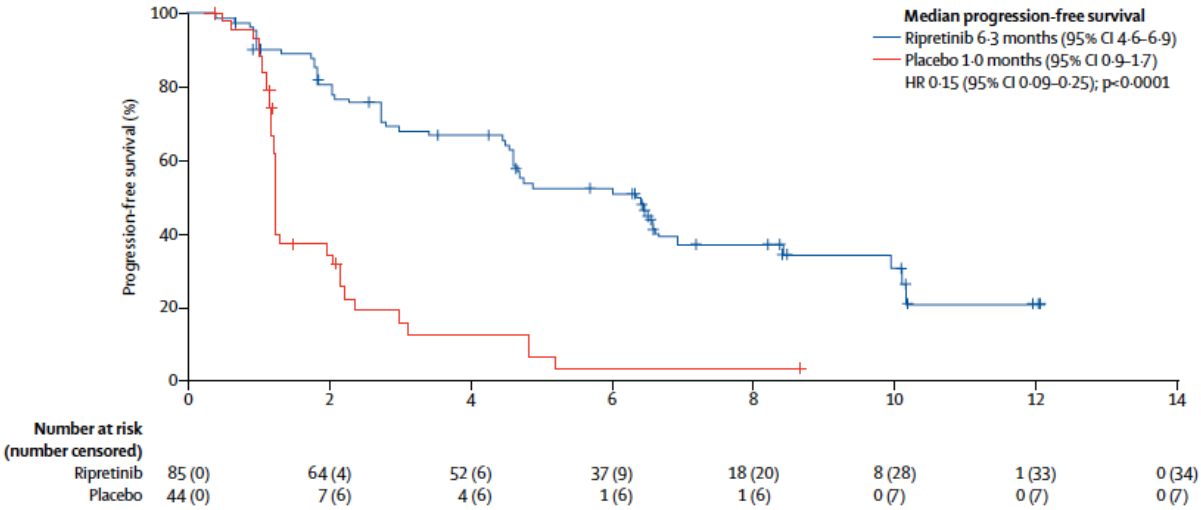
In the 43 (of 85) patients in the ripretinib group who dose escalated to ripretinib 150mg BID upon progression (Table 7), median PFS1 (time from randomisation to progression) was 4.6 months, and median PFS2 (time from first dose at 150mg BID to progression or death) was 3.7 months (CS,[1] Section B.2.7 and CS Appendix[9] E).

Table 7: PFS in INVICTUS, as assessed by BICR

Analysis set	**Data cut-off**	**N Ripr**	**N Pbo**	**Median PFS, months**		**HR (95% CI), p-value**	**Reference in CS**
				Ripr	**Pbo**		
ITT	May 2019	85	44	6.3	1.0	0.15 (0.09 to 0.25), $p<0.0001$	CS, Section B.2.6
	March 2020	85	44	6.3	1.0	0.16 (0.10 to 0.27), $p<0.0001$	CS, Section B.2.6
	January 2021	85	44	6.3	1.0	0.16 (0.10 to 0.27), $p<0.0001$	CS, Section B.2.6
Open-label **PFS2** in patients crossing over from placebo to ripretinib	Not reported	-	29	-	4.6	-	CS, Section B.2.6
Patients who dose escalated from ripretinib 150mg QD to 150mg BID: **PFS1** (time from randomisation to progression)	August 2020	43	-	4.6	-	-	CS Appendix E
Patients who dose escalated from ripretinib 150mg QD to BID: **PFS2** (time from first dose ripretinib 150mg BID to progression or death)	August 2020	43	-	3.7	-	-	CS Appendix E

Ripr - ripretinib; Pbo – placebo; BID - twice a day; BICR - blinded independent central review; CI - confidence interval; HR - hazard ratio; ITT - intention-to-treat; PFS - progression-free survival; QD - once a day; CS - company's submission

Figure 5: Kaplan-Meier plot of PFS assessed by BICR, ITT population, May 2019 cut-off (reproduced from CS, Figure 6)



BICR - blinded independent central review; CI - confidence interval; HR - hazard ratio; ITT - intention-to-treat; PFS - progression-free survival.
Note: crosses denote censoring of data. Source: Blay et al. 2020,[10] page 928, Figure 2A.

4.3.2 Overall survival (OS)

As shown in Table 8 and Figure 6, median OS at the May 2019 cut-off was 15.1 months for ripretinib versus 6.6 months for placebo (HR 0.36, 95% CI 0.21 to 0.62, *p*=not reported [NR]). At the January 2021 cut-off, median OS was 18.2 months for ripretinib versus 6.3 months for placebo (HR 0.41, 95% CI 0.26 to 0.65, *p*=NR).

As noted in Section 4.2.3, at the May 2019 cut-off, 42 of 85 patients (49%) in the ripretinib group and 29 of 44 patients (66%) in the placebo group had received open-label ripretinib after progression. The ERG's clinical advisors stated that continued ripretinib use beyond progression is likely to have extended OS.

OS for patients crossing over, or not crossing over, from placebo to ripretinib

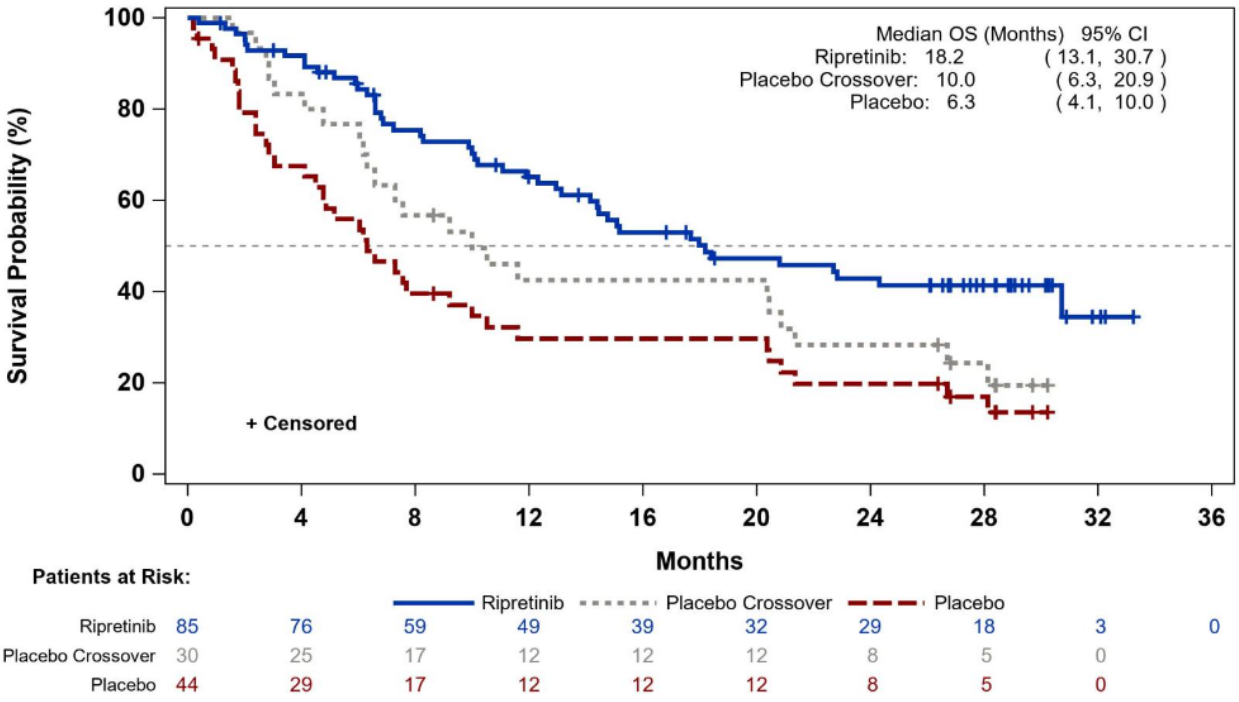
In a *post hoc* analysis, median OS in the 29 patients who crossed over from placebo to ripretinib was 11.6 months (May 2019 cut-off) or 10.0 months (January 2021 cut-off). Median OS in the 15 placebo patients not crossing over was 1.8 months (May 2019) [redacted] (January 2021 cut-off; clarification response,[2] question A9; see Figure 7).

Table 8: OS in INVICTUS

Analysis set	Data cut-off	N Ripr	N Pbo	Median OS, months		HR (95% CI)	Reference in CS
				Ripr	Pbo		
ITT	May 2019	85	44	15.1	6.6	0.36 (0.21 to 0.62)	Section B.2.6
	March 2020	85	44	Not reached	6.3	0.42 (0.26 to 0.67)	Section B.2.6
	January 2021	85	44	18.2	6.3	0.41 (0.26 to 0.65)	Section B.2.6
Patients crossing over from placebo to ripretinib	May 2019	-	29	-	11.6	-	CS Appendix E
	January 2021	-	30	-	10.0	-	CS Section B.2.6
Placebo patients who did not cross over	May 2019	-	15	-	1.8	-	CS Appendix E
	January 2021	-	[redacted]	-	[redacted]	-	Clarification response, question A9

Ripr - ripretinib; Pbo - placebo; CI - confidence interval; HR - hazard ratio; ITT - intention-to-treat; OS - overall survival; CS - company's submission

Figure 6: Kaplan-Meier plot of OS with extended follow-up, January 2021 cut-off (reproduced from CS Figure 9)



CI - confidence interval; OS - overall survival
Source: von Mehren et al. 2021,[14] slide 13 (presented at ESMO, September 16-21, 2021)

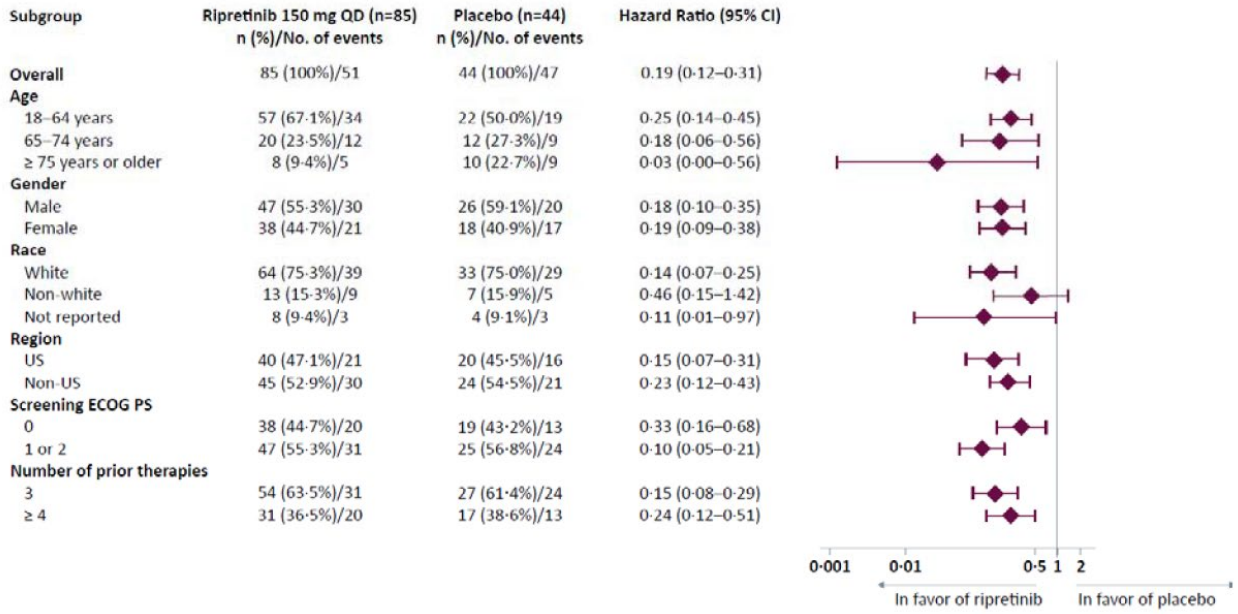
Figure 7: Kaplan-Meier plot of OS with extended follow-up, January 2021 cut-off, including placebo patients who did not switch to ripretinib (reproduced from company's clarification response, question A9)

CI - confidence interval; OS - overall survival

4.3.3 Subgroup analyses for PFS and OS

PFS: Subgroup analyses for PFS are reported in CS Appendix E;[9] these are reproduced in Figure 8. These analyses were pre-specified. Results were generally consistent across subgroups, though the small number of patients in some subgroups made interpretation difficult. The ERG requested data on PFS and OS subgrouped according to whether patients had progressed on, were resistant to, or were intolerant to prior TKIs, as suggested in the final NICE scope;[3] however the company responded that these data were not recorded (see clarification response,[2] question A8).

Figure 8: PFS in patient subgroups as assessed by BICR, ITT population, May 2019 cut-off (reproduced from CS Appendix E, Figure 1)



BICR - blinded independent central review; CI - confidence interval; ECOG - Eastern Cooperative Oncology Group; PS - performance status; ITT - intention-to-treat; PFS - progression-free survival; QD - once a day
Source: Blay et al. 2020,[10] supplementary appendix, Figure S3

OS: Subgroup analyses for OS by age and line of treatment are reported in the company's clarification response[2] (questions A6 and A7) and are shown in Table 9 (for the January 2021 data-cut). OS was comparable across age groups. [redacted].

Table 9: Subgroup analyses for OS, January 2021 cut-off (adapted from company's clarification response, questions A6 and A7)

Subgroup	Ripretinib vs placebo HR (95% CI)
Age	
18 - 64 years	[redacted]
65 - 74 years	[redacted]
75 years or older	[redacted]
Number of prior therapies	
3 prior therapies (n=54)	[redacted]
≥ 4 prior therapies (n=31)	[redacted]

CI - confidence interval; HR - hazard ratio

4.3.4 Response rates

Objective responses in the double-blind period occurred in 8 of 85 patients (9%) in the ripretinib group and in 0% of patients in the placebo group, at the May 2019 cut-off (see Table 10). All responses were partial; there were no complete responses (CRs). Compared with placebo, a higher proportion of ripretinib patients had stable disease at 6 weeks (66% versus 20%) and fewer ripretinib patients had

disease progression (19% versus 64%). At the March 2020 and January 2021 cut-offs, objective response rates were 11.8% for ripretinib versus 0% for placebo.

Table 10: Response data for INVICTUS, May 2019 cut-off (adapted from CS, Table 12)

Response	**Ripretinib (n=85): n (%)**	**Placebo (n=44): n(%)**	***p*-value**
Confirmed OR	8 (9%)	0 (0%)	0.0504
CR	0 (0%)	0 (0%)	-
PR	8 (9%)	0 (0%)	-
SD (6 weeks)	56 (66%)	9 (20%)	-
SD (12 weeks)	40 (47%)	2 (5%)	-
PD	16 (19%)	28 (64%)	-
Not evaluable	4 (5%)	3 (7%)	-
No response assessment	1 (1%)	4 (9%)	-
Median duration of response	Not reached	N/a	

BICR - blinded independent central review; CI - confidence interval; CR - complete response; ITT - intention-to-treat; OR - objective response; ORR - objective response rate; PD - progressive disease; PR - partial response; SD - stable disease; N/a – not applicable
Source: Blay et al. 2020,[10] page 929, Table 2.

4.3.5 Health-related quality of life (HRQoL)

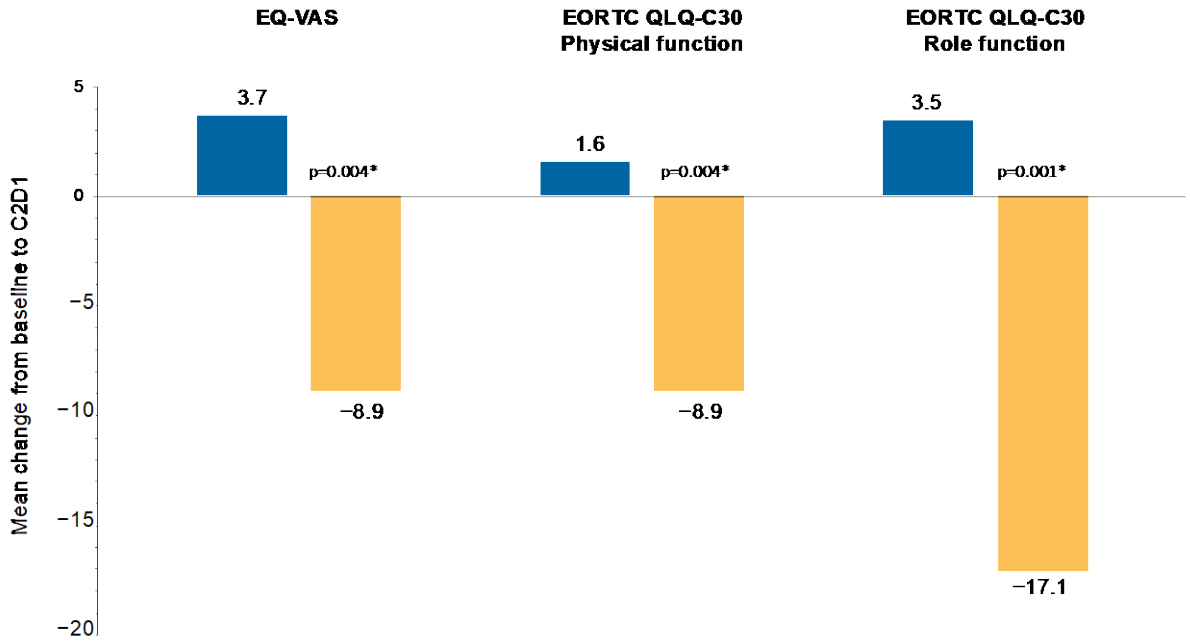
HRQoL in INVICTUS[5] was assessed using the EORTC QLQ-C30 role and physical functioning domains, the EQ-5D-5L questionnaire and the EQ-VAS (CS,[1] Section B.2.6). The ERG notes that the clinical section of the CS only reports HRQoL data from baseline to the first day of Cycle 2 (i.e., the first 29 days of treatment). The CS states that later measurements are not reported due to the low number of evaluable patients in the placebo group after this time point.

The CS[1] states that patients in the ripretinib group reported an improvement in the physical and role functioning domains of the EORTC QLQ-C30 from baseline to Cycle 2 Day 1 (see Figure 9), with an adjusted mean increase in scores (indicating improvement) of 1.6 and 3.5 points, respectively, compared with a decline of 8.9 and 17.1 points for patients in the placebo group. Patients likewise reported an improvement in HRQoL from baseline to Cycle 2 Day 1, as assessed by an adjusted mean increase in EQ-VAS scores of 3.7 versus a decline of 8.9 with placebo. The CS states that no minimal clinically important difference (MCID) for HRQoL has been established in GIST, but that assuming a MCID of 10% mean score change or score change of 5 points, the difference between ripretinib and placebo could be considered clinically meaningful. The CS[1] also reports the above HRQoL measures through to Cycle 10 in the ripretinib arm, but not the placebo arm. HRQoL on all measures appeared to remain stable on all scores through to Cycle 10 (CS, Figure 12; not reproduced here), although it was unclear to the ERG why only a small number of patients were evaluated for HRQoL at later cycles.

[redacted]

[redacted]

Figure 9: HRQoL: change from baseline to Cycle 2 Day 1, ITT population (reproduced from CS, Figure 11)



C2D1 - cycle 2, day 1; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item questionnaire; EQ-VAS - EuroQol visual analogue scale; ITT - intention-to-treat; PROM - patient-reported outcome measure
**Note: p-values are nominal*
The physical and role function questions were rolled up to a score out of 100. Change from baseline to C2D1 in EQ-VAS scores were evaluable in 70 and 32 patients in the ripretinib and placebo arm, respectively. For the EORTC QLQ-C30 physical functioning, 71 and 32 patients were evaluable in each group, respectively, and for the EORTQ QLQ-C30 role functioning, 70 and 32 patients were evaluable in each group, respectively.
Source: Heinrich et al. 2020, poster presented at ASCO [Poster 423], figure 3 and Blay et al. 2020,[10] supplementary appendix, Table S3.

4.4 Safety of ripretinib

4.4.1 Studies providing safety data on ripretinib

The CS[1] (Section B.2.10) focuses on safety data from the INVICTUS RCT.[5] The reported safety data are for the double-blind period of INVICTUS (i.e., up to disease progression), therefore the ERG notes that these data should not be affected by treatment switching after progression. The safety population included all 85 patients randomised to ripretinib and 43 of 44 patients randomised to placebo (i.e., a total of 128 of 129 randomised patients).

In terms of other sources of safety data on ripretinib, CS Appendix D.7.8[9] states that in the 29 patients who crossed over from placebo to ripretinib in the open-label phase of INVICTUS,[5] there were no new safety signals which had not already been observed in the double-blind phase. In addition, CS Appendix

D.7.8 cites a Phase 1 single-arm study (NCT02571036) in which patients with GIST received ripretinib at a dose of 150mg either QD or BID, and provides limited data on Grade 3/4 AEs.

4.4.2 Summary of safety data from INVICTUS

A summary of safety data is provided in Table 11, including additional information provided in the company's clarification response[2] (question A11). The overall frequency of treatment-emergent adverse events (TEAEs) was similar for ripretinib and placebo (99% vs 98%), whilst drug-related TEAEs were more frequent with ripretinib (85% vs. 61%). The frequency of Grade 3/4 AEs was slightly higher for ripretinib than placebo (49% vs. 44%), whilst drug-related Grade 3/4 AEs were also higher for ripretinib (25% vs. 16%). Serious AEs (SAEs) were less frequent for ripretinib (31% vs. 44%), whilst drug-related SAEs were similar in both groups (9% vs. 7%). Any AEs leading to discontinuation were slightly less frequent for ripretinib (8% vs. 12%). However, treatment-related AEs leading to discontinuation (4.7% vs. 2.3%), dose reduction (5.9% vs. 2.3%) or dose interruption (14% vs. 7%) were more frequent for ripretinib.

Table 11: Summary of TEAEs in the double-blind phase of INVICTUS, safety population (adapted from CS Table 15)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
All AEs		
Any TEAE	84 (98.8%)	42 (97.7%)
Any drug-related TEAE	72 (84.7)	26 (60.5)
Any grade 3/4 TEAE	42 (49.4%)	19 (44.2%)
Any grade 3/4 drug-related TEAE	21 (24.7)	7 (16.3)
Any treatment-emergent SAE	26 (30.6%)	19 (44.2%)
Any treatment-emergent drug-related SAE	8 (9.4)	3 (7.0)
Dose reductions and discontinuations		
Any TEAE leading to treatment discontinuation	7 (8.2%)	5 (11.6%)
Any treatment-related TEAE leading to treatment discontinuation	4 (4.7%)	1 (2.3%)
Any treatment-related TEAE leading to dose reduction	5 (5.9%)	1 (2.3%)
Any treatment-related TEAE leading to dose interruption	12 (14.1%)	3 (7.0%)
Deaths		
Any death	12 (14%)	13 (30%)
Any TEAE leading to death	5 (5.9%)	10 (23.3%)
Any treatment-related TEAE leading to death	1 (1.2%)	1 (2.3%)
Death	1 (1.2%)	0
Pulmonary oedema	0	1 (2.3%)**
Septic shock	0	1 (2.3%)**

SAE - serious adverse event; TEAE - treatment-emergent adverse event
** 44 patients randomised to placebo yet one did not receive treatment.*
*** Pulmonary oedema and septic shock were reported in the same patient.*
Source: Blay et al. 2020,[10] supplementary appendix, Table S2; von Mehren et al. 2019, presentation at ESMO (abstract LBA87 and poster); European Medicines Agency 2021, Qinlock European Public Assessment Report.[15]

4.4.3 Deaths

Deaths during the double-blind period were less frequent for ripretinib than placebo (14% vs. 30%) [redacted] (see Table 11). AEs leading to death were less frequent for ripretinib than placebo (6% vs. 23%), whilst treatment-related AEs leading to death occurred in 1 patient in each group (1.2% vs. 2.3%): 1 death was due to unknown causes in the ripretinib group, and 1 death was due to septic shock and pulmonary oedema in the placebo group.

4.4.4 AEs by type

Table 12 summarises TEAEs observed in INVICTUS.[5] The most common TEAEs (≥20%) in the ripretinib group were: alopecia (52% vs. 5%); fatigue (42% vs. 23%); nausea (39% vs. 12%); abdominal pain (37% vs. 30%); constipation (34% vs. 19%); myalgia (32% vs. 12%); diarrhoea (28% vs. 14%), decreased appetite (27% vs. 21%); palmar-plantar erythrodysaesthesia syndrome (PPES) (21% vs. 0%) and vomiting (21% vs. 7%). These were mainly Grade 1 or 2 in severity.

Table 12: TEAEs in >10% of patients in the ripretinib group compared to placebo, double-blind period (safety population) (reproduced from CS, Table 16)

TEAE	Ripretinib 150mg QD any grade (n=85)	Ripretinib 150mg QD Grade 3/4 (n=85)†	Placebo any grade (n=43)*	Placebo grade 3/4 (n=43)*†
Any TEAE or Grade 3/4 TEAE**	84 (98.8%)	42 (49.4%)	42 (97.7%)	19 (44.2%)
Alopecia	44 (51.8%)	0	2 (4.7%)	0
Fatigue	36 (42.4%)	3 (3.5%)	10 (23.3%)	1 (2.3%)
Nausea	33 (38.8%)	3 (3.5%)	5 (11.6%)	0
Abdominal pain	31 (36.5%)	6 (7.1%)	13 (30.2%)	2 (4.7%)
Constipation	29 (34.1%)	1 (1.2%)	8 (18.6%)	0
Myalgia	27 (31.8%)	1 (1.2%)	5 (11.6%)	0
Diarrhoea	24 (28.2%)	1 (1.2%)	6 (14.0%)	1 (2.3%)
Decreased appetite	23 (27.1%)	1 (1.2%)	9 (20.9%)	1 (2.3%)
PPES	18 (21.2%)	0	0	0
Vomiting	18 (21.2%)	3 (3.5%)	3 (7.0%)	0
Headache	16 (18.8%)	0	2 (4.7%)	0
Weight decreased	16 (18.8%)	0	5 (11.6%)	0
Arthralgia	15 (17.6%)	0	2 (4.7%)	0
Blood bilirubin increased	14 (16.5%)	1 (1.2%)	0	0
Oedema peripheral	14 (16.5%)	1 (1.2%)	3 (7.0%)	0
Muscle spasms	13 (15.3%)	0	2 (4.7%)	0
Anaemia	12 (14.1%)	8 (9.4%)	8 (18.6%)	6 (14.0%)
Hypertension	12 (14.1%)	6 (7.1%)	2 (4.7%)	0
Asthaenia	11 (12.9%)	1 (1.2%)	6 (14.0%)	2 (4.7%)
Dry skin	11 (12.9%)	0	3 (7.0%)	0
Dyspnoea	11 (12.9%)	0	0	0
Hypophosphataemia	9 (10.6%)	4 (4.7%)	0	0
Lipase increased	9 (10.6%)	4 (4.7%)	0	0
Pruritus	9 (10.6%)	0	2 (4.7%)	0
Stomatitis	9 (10.6%)	0	0	0

PPES - palmar-plantar erythrodysaesthesia syndrome; QD - once a day; TEAE - treatment-emergent adverse event
** 44 patients were randomised to placebo, but 1 did not receive treatment.*
*** Regardless of causality.*
† Corresponding grade 3/4 TEAEs to TEAEs in >10% of patients receiving ripretinib.
Source: von Mehren et al. 2019, presentation at ESMO; Gelderblom et al. 2020, presentation at CTOS Virtual Meeting (poster).[16]

4.4.5 Grade 3 and 4 AEs and serious AEs

Grade 3 or 4 TEAEs reported in ≥5% of patients in the ripretinib arm were: anaemia (9% vs. 14%); abdominal pain (7% vs. 5%), and hypertension (7% vs. 0%) (see Table 12). The most common Grade 3 or 4 laboratory abnormalities (≥4%) were anaemia (9% vs. 14%), increased lipase (5% vs. 0%), and hypophosphataemia (5% vs. 0%).[16]

In a Phase 1 single-arm study of ripretinib (Study NCT02571036), Grade 3 or 4 AEs occurring in >5% of patients included: increased lipase (18%); anaemia (8%) and abdominal pain (8%). Grade 3/4 increased lipase occurred in a higher percentage of patients in this study (18%) than in INVICTUS[5] (5%), whilst anaemia and abdominal pain occurred at similar rates to INVICTUS (CS Appendix D.7.8[9]).

Serious adverse reactions that occurred in >2% of patients were: abdominal pain (4.7%); anaemia (3.5%); nausea (2.4%) and vomiting (2.4%).

4.4.6 AEs of special interest

TEAEs of special interest are shown in Table 13. Squamous cell carcinoma (SCC) of the skin occurred in 2 of 85 patients (2.4%) in the ripretinib arm and 0 patients in the placebo arm, whilst actinic keratosis (dry, scaly patches of sun-damaged skin which can progress to skin cancer) occurred in 5 of 85 patients (5.9%) in the ripretinib arm and 1 of 43 patients (2.3%) in the placebo arm.

Table 13: TEAEs of special interest in double-blind period, safety population (reproduced from company's clarification response, question A12)

Preferred term	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Squamous cell carcinoma of skin	2 (2.4)	0 (0)
Actinic keratosis	5 (5.9)	1 (2.3)

Source: Deciphera Pharmaceuticals. INVICTUS CSR, 2019

As part of their clarification response[2] (question A12), the company sought UK clinical opinion on the clinical significance of these events. The clinician consulted by the company stated that the rates of actinic keratosis should always monitored closely, but with an active and well-tolerated anticancer treatment, dealing with Grade 1-2 keratosis is not a major clinical problem. Regarding SCC, the clinician stated that SCC is an important event which needs to be carefully monitored, but that in this population, the benefit of ripretinib is far greater that the disadvantage of SCC, given the low incidence in these studies. The company also noted that a dermatopathological review of cutaneous SCC (cuSCC) events in 10 ripretinib-treated GIST patients concluded that patients who developed cuSCC lesions whilst on ripretinib were elderly, with a median age of 76 years. The cuSCC lesions occurred in sun-exposed areas, did not show aggressive histopathological features, and were analogous to their lowest-risk ultraviolet-induced counterparts. Based on this analysis, the company states that the low-risk cuSCC lesions in patients treated with ripretinib can generally be managed using local interventions without the need for dosing modifications or interruptions.

4.5 Ongoing studies

Ongoing studies of ripretinib are summarised in Table 14. In addition to the INVICTUS RCT,[5] there is an ongoing double-blind Phase 3 RCT (INTRIGUE) assessing the comparative efficacy of ripretinib versus sunitinib in second-line GIST after treatment with imatinib. The CS[1] states that the results of INTRIGUE are not relevant to this submission in terms of efficacy as the trial was not conducted in the post-regorafenib fourth-line setting, and the study did not reach its primary endpoint.

In addition, there is a Phase 1 dose escalation/expansion study of ripretinib (NCT02571036) in various advanced malignancies including GIST patients in the first- and subsequent-line setting, including 83 patients at fourth- and subsequent-line. The CS[1] states that the results are not presented in the main body of the CS, as this was a Phase 1 non-randomised study with different doses and different lines of therapy. There is also a Phase 2 single-arm study of ripretinib conducted in China (NCT04282980) in patients with advanced GIST who have progressed with prior anticancer therapies. The CS does not state why this study is not presented, but it appears that no results are yet available, and this is a single-arm non-randomised study.

Table 14: Ongoing studies of ripretinib in advanced GIST (adapted from CS, Table 18)

Study identifier	Study design	Population	Intervention, comparator	Status	Rationale for why results not presented	References
NCT03353753 INVICTUS	Phase 3, double-blind, international, multicentre RCT	Advanced GIST, 3 prior anticancer therapies, including imatinib, sunitinib, and regorafenib (4L+)	Ripretinib Placebo	Active, not recruiting Estimated completion date April 2022	N/a	As earlier
NCT03673501 INTRIGUE	Phase 3, double-blind, multicentre, RCT	Advanced GIST following treatment with imatinib (2L)	Ripretinib Sunitinib	Active, not recruiting Estimated completion date March 2022	Not in 4L post-regorafenib setting. Study did not reach its primary endpoint	Nemunaitis *et al.*, 2020 (clinical trial protocol)[17, 18]
NCT02571036 FIH, Phase 1 dose escalation/ expansion study	Phase 1, open-label, FIH, single-arm study. Two phases: dose escalation phase followed by an expansion phase at the RP2D (150mg QD) to assess safety, PK, and preliminary antitumour activity	Advanced malignancies, including GIST patients in the ≥1L setting, including ≥4L (n=83)	Ripretinib N/a	Active, not recruiting Estimated completion date June 2022 (results available)	Phase 1 non-randomised study with different doses and different lines of therapy	Janku *et al.*, 2020[12] Chi *et al.*, 2019[11]
Phase 2 study in China (NCT04282980)	Phase 2, single-arm, open-label multicentre study conducted in China	Advanced GIST who have progressed with prior anticancer therapies	Ripretinib N/a	Active, not recruiting Estimated completion date June 2022	Not stated; ERG assume because single-arm non-randomised study and results not yet available	ClinicalTrials.gov[19]

1L - first-line; 2L - second-line; 4L+ - fourth- and subsequent-line; CS - company's submission; GIST - gastrointestinal stromal tumour; FDA - Food and Drug Administration; FIH - first-in-human; L - line; N/a - not applicable; PK – pharmacokinetics; QD - once a day; RCT - randomised controlled trial; RP2D - recommended Phase 2 dose

4.6 Meta-analysis

Meta-analysis was not conducted as only one study (the INVICTUS RCT[5]) was identified in the company's SLR as being relevant to the submission. The ERG agrees that meta-analysis is not required.

4.7 Indirect comparison and/or mixed treatment comparison

The CS states that no indirect or mixed treatment comparison was conducted since only one study (INVICTUS[5]) was identified in the SLR as being relevant to the submission, and included the only comparator of interest (BSC). As noted in Section 3.3, many patients continue to receive regorafenib beyond disease progression. Neither the CS[1] nor the company's clarification response[2] provides any indirect comparison of ripretinib versus continued post-progression regorafenib.

4.8 Additional work on clinical effectiveness undertaken by the ERG

The ERG investigated the impact of using fewer concepts in the search on the number of relevant trials retrieved. Removal of the "Relapsed/Refractory/Resistant" terms from the MEDLINE and Embase search gave a difference of 262 records. A screen of the records by the ERG indicated that no relevant trials were missed. The ERG also investigated the impact of field searching for imatinib or sunitinib or regorafenib. Replacement of the "ti,ab." field for ".mp." (multi-purpose) in MEDLINE and Embase resulted in 273 records. A screen of the records by the ERG indicated that no relevant records were missed.

4.9 Conclusions of the clinical effectiveness section

Methods of systematic review: The ERG considers the company's systematic review methods to be generally of a good standard. The literature searches had some limitations; however, additional searching by the ERG suggested it was unlikely that any relevant studies had been missed.

Clinical evidence: The CS presents data from the INVICTUS RCT of ripretinib plus BSC versus placebo plus BSC in 129 patients with advanced GIST who had progressed on, or were intolerant to, (at least) imatinib, sunitinib and regorafenib. The ERG's clinical advisors considered INVICTUS to be broadly representative of UK clinical practice. However, there were some differences between INVICTUS and the company's proposed use of ripretinib. The company's positioning of ripretinib is at fourth-line, whilst more than one-third of patients in INVICTUS had >3 prior therapies. In addition, the company is seeking a positive NICE recommendation for the use of ripretinib up to the point of disease progression, whilst in INVICTUS patients could receive ripretinib beyond progression and the ERG's clinical advisors stated that this is how they would want to use ripretinib in clinical practice.

At the May 2019 cut-off, median PFS was 6.3 months for ripretinib versus 1.0 months for placebo (HR 0.15, 95% CI 0.09 to 0.25, $p<0.0001$). Median OS was 15.1 months for ripretinib versus 6.6 months for

placebo (HR 0.36, 95% CI 0.21 to 0.62, *p*=NR), 11.6 months in placebo crossover patients, and 1.8 months in placebo non-crossover patients. HRQoL was only reported for both groups during the first cycle (first 29 days), during which there were improvements in the ripretinib group versus declines in the placebo group on the EQ-VAS and the EORTC QLQ-C30 (physical and role functioning domains). The most common TEAEs with ripretinib (vs. placebo) were alopecia (52% vs. 5%); fatigue (42% vs. 23%); nausea (39% vs. 12%); abdominal pain (37% vs. 30%); constipation (34% vs. 19%); myalgia (32% vs. 12%); diarrhoea (28% vs. 14%); decreased appetite (27% vs. 21%); PPES (21% vs. 0%) and vomiting (21% vs. 7%). The most common Grade 3 or 4 TEAEs were anaemia (9% vs. 14%); abdominal pain (7% vs. 5%); hypertension (7% vs. 0%); increased lipase (5% vs. 0%) and hypophosphataemia (5% vs. 0%). TEAEs of special interest included SCC of the skin (2 [2.4%] vs. 0%) and actinic keratosis (5 [5.9%] vs. 1 [2.3%]).

5. COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of ripretinib for the treatment of patients with advanced GIST after 3 prior therapies. Section 5.1 describes and critiques the company's review of existing economic evaluations. Section 5.2 describes the company's economic model and summarises the company's results. Sections 5.3 and 5.4 present the ERG's critical appraisal of the company's economic model and the results of the ERG's exploratory analyses. Section 5.5 discusses the key issues around the company's economic analysis.

5.1 Critique of company's review of existing economic analyses

5.1.1 Summary and critique of company's searches

The company performed systematic literature searches for: (i) published economic evaluations of patients who have unresectable, or advanced/metastatic GIST (CS Appendix G); (ii) HRQoL studies (CS Appendix H) and (iii) cost and resource use studies (CS Appendix I).[9] All three types of searches were undertaken in July 2020, followed by two updates in July 2021 and March 2022.

The searches for published economic evaluations and cost and resource use studies were undertaken together as a single search. The following sources were searched: MEDLINE; MEDLINE Epub Ahead of Print; In-Process & Other Non-Indexed Citations; EMBASE and the Cochrane Library. The company searched several key conference abstract websites: ASCO (2018-2021); ESMO (2017-22) and ASCO GI (2018-2021). Reference lists of retrieved systematic reviews and meta-analyses and included studies were also searched to identify further relevant studies. The company also searched four HTA agency websites in August 2021: NICE; SMC; PBAC and CADTH. The company's searches are transparent and fully reported.

The economic search strategy comprised the disease terms for GIST combined with the cost-effectiveness, cost-utility analysis, budget impact analysis, costs and resource allocation search filters (CS Appendix G.1.5.1[9]). The ERG identified errors in the search strategy whereby statements 33-37 of the search are missing and a Boolean logic statement, which should be written "or/8-32", is also missing. Therefore, the "ECON Outcomes in Patients with GIST" combined search appears to be incorrect. It is unclear to the ERG whether this is a reporting error or whether it reflects an error in the implemented search. The ERG notes that if this error applies to the implemented search, it will have had a negative impact on search recall.

5.1.2 Summary and critique of company's review of existing economic evaluations

The inclusion criteria for the company's review of published economic evaluations are reported in Table 1 of CS Appendix G.[9] Studies were eligible for inclusion in the review if the population included in the analysis related to people with advanced, metastatic or unresectable GIST at any line of treatment. The

inclusion criteria also specified that studies must be economic evaluations, budget impact analyses, or burden of illness studies, or must report measures of costs and/or health care resource use. No restrictions were applied to the interventions or comparators assessed within the studies. Editorials, reviews, comments, and letters were excluded, as were studies not published in the English language and studies published prior to 2000.

Across the original and update searches, a total of 32 records from 29 unique studies were included in the review. Of these, 23 were cost-effectiveness/cost-utility analyses, three were budget impact analyses and the remaining six were health care resource use studies. A summary of the included economic evaluations is presented in Table 20 of the CS.[1] The company's quality assessment of the included economic evaluations using the Drummond checklist[20] is provided in Tables 4 and 5 of CS Appendix G.3.[9] The results of this quality assessment are presented in tabular form only; a narrative summary of the quality of the included studies is not provided.

The economic analyses included in the company's review used a variety of modelling approaches, including state transition, partitioned survival and simulation models. Treatments evaluated included surgical resection, imatinib, sunitinib, regorafenib, ripretinib, pazopanib and standard care (including no treatment, BSC, palliative care and placebo). Studies were conducted in various settings including: Brazil; Canada; China; England; Germany; France; Mexico; Singapore; Spain; Turkey and the US.

CS Appendix[9] G.3 (page 71) states that *"There were no relevant CEAs of ripretinib in patients with 4L+ GIST selected in the economic SLR."*[9] However, this statement is not accurate, as one of the included studies (Liao *et al.*[21]) evaluated ripretinib versus placebo as a fourth- or subsequent-line treatment for the treatment of advanced GIST. Liao *et al.* reports the methods and results of a health economic model in which parametric survival models were fitted to replicated individual patient data (IPD) from the INVICTUS trial.[5] The authors state that the model uses a Markov approach; however, the survival model parameters relate to the endpoints PFS and OS, which indicates that the model is a partitioned survival analysis. The analysis did not include statistical adjustment of OS data to account for confounding resulting from placebo group patients switching onto ripretinib; instead, the costs of post-progression ripretinib (after switching) were included in the total costs for the BSC group. Health state utility values were taken from analyses of EQ-5D-3L data collected in the GRID trial (regorafenib versus placebo in patients with metastatic/unresectable GIST who have progressed on or were intolerant to imatinib and who have progressed on sunitinib).[22, 23] The authors report an incremental cost-effectiveness ratio (ICER) for ripretinib versus placebo of US$244,010 per quality-adjusted life year (QALY) gained. The ERG is unsure why this study has not been discussed in the CS,[1] as it appears to be directly relevant to the decision problem. The ERG notes however that a key limitation of the analysis by Liao *et al.* is the absence of any statistical adjustment for potential confounding of OS data due to treatment switching.

5.2 Summary of the company's submitted economic analysis

5.2.1 Scope of the company's economic analyses

As part of their submission to NICE,[1] the company submitted an executable health economic model programmed in Microsoft Excel.® The scope of the company's economic analysis is summarised in Table 15.

Table 15: Scope of the company's economic analysis

Population	Patients with advanced GIST after 3 therapies including imatinib, sunitinib and regorafenib
Time horizon	40 years (lifetime)
Intervention	Ripretinib 150mg QD (administered orally)
Comparator	BSC
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2019/2020 (except drug costs which reflect current prices)

GIST - gastrointestinal stromal tumour; mg - milligram; QD - once a day; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services; BSC - best supportive care

The company's economic model assesses the cost-effectiveness of ripretinib (plus BSC) versus BSC alone for the treatment of patients with advanced GIST after at least three therapies, including imatinib, sunitinib and regorafenib. Cost-effectiveness is assessed in terms of the incremental cost per QALY gained from the perspective of the NHS and Personal Social Services (PSS) over a 40-year (lifetime) horizon. Unit costs are valued at 2019/20 prices, except for drug acquisition costs which are valued at current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Population

The company's economic analysis is intended to reflect the population of patients with advanced GIST who have received three prior therapies (i.e., the company intends to position ripretinib as fourth-line therapy). Patient characteristics are based on patients enrolled in the INVICTUS trial.[5] At model entry, patients are assumed to be 60.1 years of age and 43.41% of patients are assumed to be female.

As noted in Section 4.2.3, more than one-third of patients in INVICTUS[5] had already received at least four prior lines of treatment at study entry (see Table 6). The ERG's clinical advisors commented that the number of prior therapies received is likely to be prognostic of outcomes. The company's intended positioning of ripretinib is not fully consistent with the evidence used to inform the model, as the outcomes for patients who have received at least three prior therapies in INVICTUS may not reflect expected outcomes in patients who have received exactly three prior therapies in usual clinical practice. This issue is discussed further in Section 5.3.5.

Intervention

The intervention included in the company's economic analyses is ripretinib, administered orally at a dose of 150mg (taken as 3 x 50mg tablets) daily. This is in line with the final NICE scope[3] and the EMA/MHRA marketing authorisation for ripretinib.[4] The SmPC for ripretinib[4] (page 2) states that *"treatment with QINLOCK should continue as long as benefit is observed or until unacceptable toxicity."* In contrast, the company's base case model assumes that all patients will discontinue treatment with ripretinib at the point of disease progression. The company's clarification response[2] (question A2) states that *"The company are seeking reimbursement for the use of ripretinib only up to the point of disease progression."* The base case model does not include any adjustment of the OS data from INVICTUS[5] to account for the potential additional benefit of continued ripretinib treatment received after disease progression. This is a key issue which is discussed further in Section 5.3.5. The model assumes that patients do not receive any further active anticancer treatment after progressing on ripretinib (i.e., they receive BSC alone).

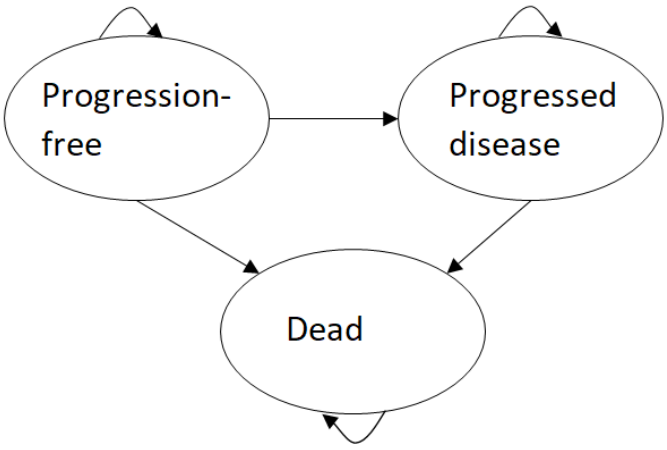
Comparators

The company's base case analysis includes a single comparator: BSC (no active therapy). The economic model includes BSC costs associated with: pain management (analgesics); computerised tomography (CT) and magnetic resonance imaging (MRI) scans; full blood counts (FBCs) and liver function tests (LFTs); outpatient appointments; palliative resection; palliative radiotherapy (RT); the management of AEs and end of life care (see Section 5.2.4).

5.2.2 Model structure and logic

The company's economic model adopts a partitioned survival approach, including three health states: (i) progression-free; (ii) progressed disease, and (iii) dead (see Figure 10).

Figure 10: Company's model structure



The model logic operates as follows. Patients enter the model in the progression-free state and receive treatment with either ripretinib (plus BSC) or BSC alone. At any time *t*, health state occupancy is determined by the cumulative probabilities of OS and PFS, whereby: the probability of being alive and progression-free is given by the cumulative probability of PFS; the probability of being alive following disease progression is calculated as the cumulative probability of OS minus the cumulative probability of PFS, and the probability of being dead is calculated as one minus the cumulative probability of OS. The company's model includes half-cycle correction, although this is subject to an error (see Section 5.3.5). Patients in the ripretinib group are assumed to continue to receive treatment until progression or death, whichever occurs first; time to treatment discontinuation (TTD) is thus assumed to be equivalent to PFS. No further active anticancer treatments are assumed to be given after disease progression in the ripretinib group, or to any patient in either health state in the BSC group.

The cumulative probabilities of OS and PFS for patients receiving ripretinib and BSC are modelled using parametric survival distributions fitted to time-to-event data from the INVICTUS trial.[5] The model applies a structural constraint whereby if the risk of death from the parametric survival model is lower than that for the age- and sex-matched general population (based on Office for National Statistics [ONS] life tables[24]) in any given cycle, the model applies the general population mortality risk, otherwise the unadjusted cumulative OS probability is used. The ERG believes that this aspect of the model is subject to an error (see Section 5.3.5). No other structural constraints are included in the model.

HRQoL is assumed to be determined by the presence/absence of disease progression. The utility values applied in the progression-free and progressed disease states are based on EQ-5D-5L data (mapped to the 3L version) collected in INVICTUS.[5, 25] The same utility values are applied in each treatment group. Utility values are not adjusted for increasing age. The model also includes short-term QALY losses associated with Grade 3/4 TEAEs occurring in ≥5% of either group in INVICTUS, estimated using disutility values reported in other literature.[26, 27] All TEAEs are assumed to have a duration of one model cycle (approximately 28 days).

The model includes costs associated with: (i) drug acquisition; (ii) health state management (scans, tests and outpatient visits); (iii) pre-treatment resource use (scans and tests); (iv) palliative treatments; (v) the management of AEs and (iv) end of life care costs. Drug acquisition costs for ripretinib are modelled as a function of the PFS distribution, treatment compliance, relative dose intensity (RDI) and unit costs. BSC pain management costs and health state costs are applied in each cycle. Palliative treatment costs are applied once in the first model cycle and once again at the point of disease progression. Other costs are applied once only at specific timepoints - either at model entry, on disease progression or at the point of death.

The incremental health gains, costs and cost-effectiveness for ripretinib versus BSC are estimated over a 40-year time horizon using a 28.10-day cycle duration (1/13th of a year). No economic subgroup analyses are presented in the CS.[1]

5.2.3 Key assumptions employed in the company's model

The company's economic model employs the following key assumptions:

- The modelled population is 60.10 years of age at model entry.[5]
- The model includes a stopping rule whereby ripretinib is assumed to be discontinued in all patients at the point of disease progression (hence, TTD is assumed to be equal to PFS). Patients do not go on to receive further active treatments after progressing on ripretinib.
- BSC is the sole comparator for ripretinib.
- Independently fitted log-normal distributions are used to model both PFS and OS.
- The model includes a structural constraint which attempts to prevent the mortality risk with GIST being lower than that for the age- and sex-matched general population (although the ERG believes that this has been implemented incorrectly). No other constraints are included. Given the use of a partitioned survival approach, the risks of progression and death are structurally unrelated.
- Continued ripretinib use after progression is assumed not to have resulted in confounding of OS data; hence, no adjustment is included in the company's base case analysis.
- HRQoL is determined by the presence/absence of disease progression. The same utility values are applied to the health states in each treatment group. The utility value for the progression-free state is slightly higher than the value applied in the progressed disease state. Utility values are not age-adjusted or capped by general population utility values.
- AEs result in QALY losses and additional costs. These are assumed to be resolved within 1 model cycle.
- Prior to disease progression, pre-treatment and disease management costs are assumed to be higher for patients receiving ripretinib compared with those receiving BSC alone. The same costs per cycle/event for pain management, the management of progressed disease, palliative treatments and end of life care are applied to the ripretinib and BSC groups.

5.2.4 Evidence used to inform the company's model parameters

Table 16 summarises the evidence sources used to inform the model parameters in the company's base case analysis. The derivation of the model parameter values is discussed in detail in the subsequent sections.

Table 16: Summary of evidence used to inform the company's base case analyses

Parameter / group	Ripretinib	BSC
Patient characteristics (age and sex)	INVICTUS[5]	
PFS	Log-normal model fitted to ripretinib group PFS data from INVICTUS[5]	Log-normal model fitted to placebo group PFS data from INVICTUS[5]
OS	Log-normal model fitted to ripretinib group OS data from INVICTUS[5]	Log-normal model fitted to BSC group OS data from INVICTUS,[5] adjusted for treatment switching using the simple 2-stage method
TTD	Assumed to be equivalent to PFS for ripretinib group	N/a
General population mortality	ONS life tables for the UK[24]	
Health state utility values	EQ-5D-5L data collected in INVICTUS[5] mapped to the 3L version using Van Hout *et al.*[25]	
TEAE frequencies	Grade 3/4 TEAEs arising in ≥5% of patients in either group in INVICTUS[5]	
TEAEs disutilities	Harrow *et al*.,[26] Doyle *et al.*[27] and assumptions	
TEAE duration	Assumption	
Drug acquisition costs	The list price and PAS discount were provided by the company.[1] Compliance and RDI estimates were taken from INVICTUS[5]	N/a
BSC pain management costs	Usage based on physician survey undertaken to inform NICE TA488 (regorafenib for GIST),[28] with additional information on dosing taken from NICE ID1626 (avapritinib for GIST).[7] Drug acquisition costs were taken from the BNF.[29] The commonly prescribed dosage form of each product was determined using Prescription Cost Analysis data.[30]	
Health state costs	Resource use was based on physician survey undertaken to inform TA488.[28] Unit costs were taken from NHS Reference Costs 2019/20.[31]	
Pre-treatment costs		
Palliative treatment costs		
TEAE management costs	NHS Reference Costs 2019/20[31]	
End of life care costs	The location and cost of death was taken from Abel *et al.*[32] Costs were uplifted to current prices using HCHS/NHSCII indices.[33, 34]	

BSC - best supportive care; PFS - progression-free survival; OS - overall survival; TTD - time to treatment discontinuation; ONS - Office for National Statistics; TEAE - treatment-emergent adverse event; EQ-5D-5L - Euroqol 5-Dimensions 5-level; 3L - 3-level; N/a - not applicable; TA - Technology Appraisal; BNF - British National Formulary; HCHS - Hospital and Community Health Services; NHSCII - NHS Cost Inflation Index

Time-to-event parameters

Statistical adjustment of OS data to account for treatment switching

As discussed in Section 4.2.2, within both groups of the INVICTUS trial,[5] a change in treatment could occur following disease progression. Patients who were randomised to receive placebo had the option to commence treatment with ripretinib (150mg QD) after progression. Patients who were randomised to receive ripretinib (plus BSC) could remain on treatment at the current dose (150mg QD), increase their dose (to 150mg BID) or discontinue ripretinib. The decision to remain on ripretinib (at either the current or increased dose), was informed by the investigator's view of whether the patient was receiving

benefit from ripretinib, and if dose escalation could be tolerated (see clarification response,[2] question B3). An overview of the treatment changes that occurred during the trial is provided in Table 5. The company's base case analysis includes adjustment for switching in the BSC group, but not for continued post-progression treatment in the ripretinib group; the latter is considered in the company's scenario analyses. The subsequent sections describe the results of the company's switching analysis.

Adjustment of OS data in the placebo group

Of the 44 patients in the placebo arm, 30 patients (68%) crossed over to receive ripretinib following disease progression, with the majority of switches occurring less than four weeks (one model cycle) after disease progression (mean [redacted] weeks; clarification response,[2] question B2). NICE Decision Support Unit (DSU) Technical Support Document (TSD) Number 16[35] details three main approaches which may be considered to adjust estimates of OS for treatment switching: (i) inverse probability of censoring weights (IPCW); rank preserving structural failure time model (RPSFTM); and two-stage methods. All three approaches are discussed in the CS,[1] although the IPCW was not considered for formal analysis by the company due to the small sample size and large proportion of patients switching. The other two methods, the RPSFTM and two-stage estimation approaches, were both explored. An RPSFTM was implemented using the *rpsftm* package in R. This approach relies on the "common treatment effect" assumption, which in this case, assumes that the delay in receiving ripretinib observed in the subset of placebo group patients who crossed over in INVICTUS (compared to the ripretinib arm) has not influenced survival outcomes. A plot of counterfactual event times provided in the CS (Figure 21) was used to assess this assumption; this plot suggests that the common treatment effect assumption is likely to be violated.

The two-stage approach (with re-censoring) was used in the company's base case economic analysis. This approach relies on there being an appropriate secondary baseline at the point of treatment switching, with no unmeasured confounding at this point. Time of disease progression was taken as the secondary baseline, with measurements of covariates that were closest to this time point used in the analyses. Two models were considered for the two-stage approach: a 'simple' model in which the only covariate was time to progression, and a 'complex' model which also included age, quality of life (measure not stated), and ECOG PS. Median switching-adjusted OS for the placebo arm was [redacted] and [redacted] weeks for the simple and complex models, respectively. The company used the simple model for its base case analysis on the basis that time to progression was the only statistically significant variable in the complex model and retaining additional variables would add to uncertainty (see clarification response,[2] question B5).

The CS[1] reports the results of scenario analyses using six methods of statistical adjustment of OS data to account for treatment switching from placebo to ripretinib. These include the simple two-stage

approach, the complex two-stage approach and the RPSFTM; each approach was applied separately with and without re-censoring. The results of these scenario analyses including the ripretinib PAS are reproduced in Table 29 (company's base case analysis and Scenario S11-S15). Estimates of cost-effectiveness were not sensitive to the method chosen, with the ICER for ripretinib versus BSC ranging from £49,360 to £50,717 per QALY gained.

In response to a request for clarification from the ERG (see clarification response,[2] question B4), the company provided additional information on the approach used to implement the two-stage method. The analyses provided used a log-normal model, which had the lowest Akaike Information Criterion (AIC) value of the five parametric survival models considered (exponential, log-normal, log-logistic, Weibull, and generalised gamma). Estimates of switching-adjusted median OS for placebo from the exponential model lacked face validity, whilst estimates from other models showed little variation: compared with the log-normal model estimate of [redacted] weeks, estimates for the other models ranged from [redacted] to [redacted] weeks. The impact of these on cost-effectiveness estimates was not explored, but this is not expected to be a large driver.

Seven patients in the placebo group had censored times of disease progression. When performing the statistical adjustment of OS data to account for treatment switching, these patients were assumed to have an observed progression time equal to their censored progression time. In response to request for clarification from the ERG (see clarification response,[2] question B6), the company stated that of these seven patients, three had crossed over to ripretinib treatment.

Adjustment of OS data in the ripretinib group

In response to a request for clarification from the ERG (see clarification response,[2] question A5), the company stated that, as of August 2020, 43 of the 65 patients (66%) in the ripretinib arm of INVICTUS[5] who had progressed experienced an increase in drug dosing. It is unclear how many of the remaining 22 patients continued on ripretinib without an increase in dose, although as of May 2019, 42 patients had moved to open-label ripretinib after progression (see Figure 4). As noted in Section 3.2, the company's clarification response[2] (question A2) confirms that they are seeking a positive NICE recommendation for ripretinib only up to the point of disease progression. The base case analysis submitted by the company does not adjust OS data to account for continued ripretinib use post-progression. The CS[1] does not include a description of any methods employed in scenario analyses to account for the impact of continued ripretinib post-progression use on OS. However, Table 45 of the CS (reproduced in Table 29, Scenario S16, including the ripretinib PAS) shows the impact on cost-effectiveness results of performing a simple two-stage approach with re-censoring. Including the ripretinib PAS, the ICER for ripretinib versus BSC almost doubled from the base case estimate when OS adjustment is included in the ripretinib group (base case ICER = £49,441 per QALY gained;

Scenario S16 ICER = £93,739 per QALY gained). This increase was primarily driven by a marked decrease in the survival gain (from [redacted] to [redacted] incremental life years gained [LYGs]) which consequently reduces the QALY gain (incremental QALYs = [redacted] versus [redacted]).

The company's clarification response[2] (question B5) provides further information on the OS adjustment in the ripretinib group. The company's response states that they considered both a simple and complex model for the two-stage approach, with the same covariates as for the placebo group switching analysis. As with the placebo group switching analysis, time to progression was the only statistically significant covariate, which the company used to justify the use of the simple model. Whilst the impact of using the complex model is not presented, the resulting median OS estimate of [redacted] weeks is closer to the unadjusted estimate of 79.1 weeks than it is to the simple model estimate of [redacted] weeks (see clarification response, question B5, Table 9). Hence, the ICER resulting from the complex approach is likely to be closer to that from the base case analysis than the ICER reported for Scenario S16. In their response to clarification question B5, the company also provided median OS for the simple two-stage approach using alternative model specifications. Compared with the log-normal model, estimates for other plausible models (Weibull, log-logistic and generalised gamma) ranged from [redacted] to [redacted] weeks. The impact of these alternative model specifications on estimates of cost-effectiveness was not explored. The impact of not using re-censoring was not explored.

Summary of parametric survival model fitting process and model selection

The company fitted a series of parametric survival models to the time-to-event data on PFS and OS (adjusted for treatment switching in placebo group) from INVICTUS.[5] The data-cut-off for PFS and OS was the 15th January 2021 (see clarification response,[2] question B1). The company's base case model does not include any adjustment of OS for continued treatment with ripretinib beyond progression in the intervention group, although this is considered in the company's scenario analyses (see Section 5.2.6, Table 29).

The same general survival modelling approach was applied to both the PFS data and the switching-adjusted OS data. For each endpoint, the company assessed the proportional hazards (PH) assumption to determine whether it is reasonable to fit models which include a treatment-indicating covariate (an HR). This was done by examining log-cumulative hazard plots, plotting Schoenfeld residuals and performing Schoenfeld global tests. There was evidence to suggest that the PH assumption was violated for PFS, but that it may be a reasonable assumption for OS. The company elected not to use jointly fitted models and instead fitted models independently to the data for each treatment group. The company fitted six standard parametric survival models, including the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. More flexible parametric survival distributions, such as restricted cubic spline (RCS) models, were not considered.

The CS[1] states that model selection included consideration of relative goodness-of-fit statistics using the AIC and the Bayesian Information Criterion (BIC) and visual inspection of the fitted models. The CS also mentions that the same distribution was selected for both treatment groups. The CS does not present empirical or modelled hazard plots. In addition, whilst the CS (page 57) mentions that model selection included the consideration of clinical plausibility, no evidence for this is presented in the CS, and the company's clarification response[2] (question B7) confirms that models were selected solely on the basis of visual and statistical goodness-of-fit.

PFS

Comparisons of the observed Kaplan-Meier survival functions and parametric survival model predictions for PFS are shown in Figure 11. AIC and BIC statistics for the fitted models are summarised in Table 17. The log-normal distribution was the best-fitting model in the ripretinib group, whilst the log-logistic distribution was the best-fitting model in the BSC group. When combined (based on the sum of the AIC/BIC statistics across both treatment groups), there was little difference in goodness-of-fit between the log-normal and log-logistic distributions. The company selected the log-normal distribution for inclusion in the base case analysis for both treatment groups. The reasons for the selection of this model are not fully clear from the CS.[1] As noted in Section 5.2.3, TTD is assumed to be equal to the PFS distribution for the ripretinib group.

Figure 11: Kaplan-Meier plots and parametric models, PFS (reproduced from CS, Figure 18)

BSC - best supportive care; KM - Kaplan-Meier
Company's base case log-normal model shown as solid and dashed red lines

Table 17: AIC and BIC statistics, PFS (adapted from CS, Table 23)

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					
Weibull						
Gompertz						
Log-normal						
Log-logistic						
Generalised gamma						

BSC - best supportive care; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best fitting model indicated in bold

OS

Comparisons of the observed Kaplan-Meier survival functions and parametric survival model predictions for OS are shown in Figure 12. AIC and BIC statistics for the fitted models are summarised in Table 18. Based on the AIC, the log-normal distribution was the best-fitting model in the ripretinib group, whilst the log-logistic distribution was the best-fitting model in the BSC group. Based on BIC, the exponential model was the best-fitting model in the ripretinib group whereas the log-logistic model was the best-fitting model in the BSC group. When combined (based on the sum of the AIC/BIC statistics across both groups), the log-logistic model provided the lowest AIC, whereas the exponential model provided the lowest BIC. The company selected the log-normal distribution for inclusion in the base case analysis on the basis of AIC and visual fit to the data.

Figure 12: Kaplan-Meier plots and parametric models, OS including switching adjustment in the placebo group (reproduced from CS, Figure 25)

BSC - best supportive care; KM - Kaplan-Meier
Company's base case log-normal model shown as solid and dashed red lines

Table 18: AIC and BIC statistics, OS (adapted from CS, Table 26)

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					
Weibull						
Gompertz						
Log-normal						
Log-logistic						
Generalised gamma						

BSC - best supportive care; AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Best fitting model indicated in bold

Summary of predictions of selected parametric survival models for TTD, PFS and OS

The overall model predictions of TTD, PFS and OS in the company's base case model are shown together in Figure 13. The ERG has concerns regarding the clinical plausibility of the company's model predictions of OS for the ripretinib group; these are discussed in Section 5.3.5.

Figure 13: Company's base case model predictions of TTD, PFS and OS*

[redacted]

BSC - best supportive care; TTD - time to treatment discontinuation; PFS - progression-free survival; OS - overall survival
** Includes general population mortality constraints*

Health-related quality of life

Health state utility values were informed by EQ-5D-5L data collected in the INVICTUS trial.[5] According to the CS,[1] [redacted]. The EQ-5D-5L data were mapped to the 3L version using the algorithm reported by Van Hout *et al.*[25] The dataset used to inform health state utility values included only those patients who had a recorded date of disease

progression; other patients were excluded.[1] The CS does not provide justification for excluding these patients. Utility values for each health state appear to be based on raw mean values across all patients and all timepoints. The CS reports utility values of [redacted] (SD [redacted]) for the progression-free state and [redacted] (SD [redacted]) for the progressed disease state. It is unclear from the CS whether the reported SDs account for multiple observations from the same patients.

Disutility values for AEs were taken from external sources. According to the CS,[1] the disutility value for anaemia was based on a Short Form 6-Dimensions (SF-6D) value reported by Harrow *et al.,*[26] which was then re-scaled to the EQ-5D using a method previously described by Hoyle *et al.*[36] Despite scrutinising each of these sources, the ERG was unable to determine how this re-scaling was done or how the resulting disutility value was estimated. The disutility value for abdominal pain was based on an EQ-5D VAS estimate for chest pain in lung cancer reported by Doyle *et al.*[27] The CS states that the disutility for hypertension was also taken from Doyle *et al.*, although the ERG notes that this study does not report values for this type of AE; it appears that the company has assumed that the disutility for hypertension is equivalent to that for chest pain. Whilst this assumption has been applied in previous appraisals (e.g., NICE TA439), the justification for assuming hypertension and chest pain have equivalent HRQoL impacts is unclear.

The health state utility values and AE-related disutility values applied in the company's economic model are summarised in Table 19.

Table 19: Health utility values and disutility values applied in base case analysis

Health state	Mean utility (SD)	Source and method
Progression-free	[redacted]	EQ-5D-5L estimates from INVICTUS[5] (mapped to 3L version using Van Hout *et al.*[25])
Progressed disease	[redacted]	
AE disutility		
Anaemia	-0.085 (NR)	Harrow *et al.*[26] - SF-6D disutility in Women's Health Initiative survey rescaled to EQ-5D*
Abdominal pain	-0.069 (NR)	Doyle *et al.*[27] - EQ-5D VAS for hypothetical lung cancer states valued by 101 members of the general population
Hypertension	-0.069 (NR)	

AE- adverse event; SD - standard deviation; EQ-5D-5L - Euroqol 5-Dimensions (5-level); SF-6D - Short Form 6-Dimensions; NR - not reported; VAS - visual analogue scale
**Derivation methods unclear from CS*

Resource use and costs

The model includes the following cost components: (i) drug acquisition; (ii) health state management; (iii) pre-treatment resource use; (iv) palliative treatments; (v) the management of AEs and (iv) end of life care costs. A summary of the model cost parameters is shown in Table 20. The derivation of these costs is presented in further detail in the sections below.

Table 20: Summary of model cost parameters

Cost item	Ripretinib	BSC	ERG comments

Ripretinib drug acquisition cost (per 28-day cycle)	Excluding PAS [redacted] Including PAS [redacted]	N/a	Includes mean compliance* of [redacted] and mean RDI of [redacted] from INVICTUS.[5]
BSC costs (pain management), PF state (per 28-day cycle)	£17.35		Based on drug usage from physician survey used in TA488[28] and dosing assumptions from ID1626.[7] Drug costs taken from BNF.[29] The model assumes BSC compliance and RDI values of 1.0.
BSC costs (pain management), PD state (per 28-day cycle)	£25.08		
Health state costs, PF state (per 28-day cycle)	£198.83	£159.93	Based on physician survey used to inform TA488[28] and ID1626.[7] Unit costs from NHS Reference Costs 2019/20.[31]
Health state costs, PD state (per 28-day cycle)	£224.00		
Pre-treatment scans and tests costs (once-only in first cycle)	£116.73	£30.40	
Palliative RT and palliative resection costs (applied once in first cycle and again on disease progression)	£425.93		
AE management costs (once-only in first cycle)	£172.25	£137.23	AE frequencies from INVICTUS.[5] Unit costs from NHS Reference Costs 2019/20.[31]
End of life care costs (once-only on death)	£9,634.90		Taken from NICE TA488[28] and inflated to 2021 prices using HCHS/NHSCII indices.[33, 34]

BSC - best supportive care; PAS - Patient Access Scheme; N/a - not applicable; RDI - relative dose intensity; TA - Technology Appraisal; PF - progression-free; PD - progressed disease; AE - adverse event; RT - radiotherapy; HCHS - Hospital and Community Health Services; NHSCII - NHS Cost Inflation Index; N/a - not applicable
**Defined as total number of days dosed divided by treatment duration in days*

Drug acquisition costs (per cycle, ripretinib group only)

The list price per pack of 90 x 50mg ripretinib tablets is £18,400. The total acquisition costs for ripretinib are calculated in the model as a function of the list price of ripretinib, the probability of being progression-free in each cycle, the number of days per cycle, a mean treatment compliance probability of [redacted], and a mean RDI of [redacted] from INVICTUS.[5] The resulting acquisition cost for ripretinib per 28-day cycle is estimated to be [redacted]. As ripretinib is an oral therapy, no administration costs are assumed. In addition, no wastage is assumed.

A Patient Access Scheme (PAS) has been agreed for ripretinib; this was agreed after the ERG received the CS.[1] This takes the form of a simple price discount of [redacted]. The acquisition cost for ripretinib per 28-day model cycle including the PAS is estimated to be [redacted].

BSC pain management costs (per cycle, both treatment groups)

BSC pain management costs were based on a survey of 15 physicians in England and Wales undertaken to inform NICE Technology Appraisal (TA) Number 488 (regorafenib for GIST),[28] with additional information on dosing taken from NICE ID1626 (avapritinib for GIST).[7] The physician survey was

initially conducted in 2013 and was later re-validated by two consultant oncologists in 2016. Drug costs were taken from the British National Formulary (BNF).[29] The most commonly prescribed dosage form of each product was determined using Prescription Cost Analysis data. The CS[1] states that costing was based on the maintenance doses described in the SmPC[4] for the most common indication of each product. Where a range of doses was available, the CS states that the lowest dose was assumed. A breakdown of the pain management drug cost calculations is shown in Table 21.

Table 21: Pain management drug costs

Drug, dose	% PF	% PD	Unit	Units per pack (N)	Cost per pack	Cost per unit	PF cost per 28-day cycle	PD cost per 28-day cycle
Co-codamol, 2 tablets (30/500mg) QDS	18.0%	22.0%	30/ 500mg tablet	100	£4.00	£0.040	£1.61	£1.97
Tramadol capsules, 100mg QDS	12.0%	14.0%	50mg capsule	100	£2.73	£0.027	£0.73	£0.86
Paracetamol tablets, 1g QDS	33.0%	38.0%	500mg tablet	32	£0.76	£0.024	£1.76	£2.02
Morphine sulfate immediate release tablets, 30mg every 4 hours	20.0%	29.0%	10mg tablet	56	£5.31	£0.095	£3.19	£4.62
			20mg tablet	56	£10.61	£0.19	£6.37	£9.23
Dexamethasone, 4mg QD	11.0%	19.0%	4mg tablet	50	£60.01	£1.200	£3.70	£6.39
Total cost	-	-	-	-	-	-	**£17.35**	**£25.08**

N - number; PF - progression-free; PD - progressed disease; mg - milligram; QDS - four times a day; QD - once a day

Health state costs (per cycle, both treatment groups)

Health state costs are assumed to include CT and MRI scans, FBCs, LFTs and outpatient appointments. The frequency of each resource item was based on the physician survey used to inform NICE TA488.[28] Unit costs were taken from NHS Reference Costs 2019/20.[31] The total health state costs applied in each model cycle are shown in Table 22.

Pre-treatment costs (once-only, both treatment groups)

Pre-treatment costs are assumed to include CT scans, MRI scans, FBCs and LFTs. Usage of these resource items were also taken from the physician survey used to inform TA488.[28] Unit costs were taken from NHS Reference Costs 2019/20[31] (these are the same as those used for the health state costs described above). Total pre-treatment costs are shown in Table 23. These costs are applied in the first model cycle only.

Palliative treatment costs

The model assumes that a proportion of patients will receive palliative resection and/or palliative RT. Again, the proportion of patients receiving these treatments were taken from the physician survey used to inform TA488.[28] Unit costs were taken from NHS Reference Costs 2019/20.[31] Total palliative treatment costs are shown in Table 24. These costs are applied to all patients in the first cycle and to the number of new patients with disease progression in each model cycle.

Costs of managing AEs

The model includes the costs of managing Grade 3/4 TEAEs which occurred in ≥5% of patients in either group in the INVICTUS trial.[5] Unit costs were taken from NHS Reference Costs 2019/20.[31] The total expected costs of managing AEs for ripretinib and BSC are shown in Table 25. The total costs of managing AEs are applied once only in the first model cycle.

Table 22: Health state costs per model cycle

Item	Resource use per 28-days			Unit cost	Expected cost			NHS Reference Costs codes
	Ripretinib PF	BSC PF	Both groups PD		Ripretinib PF	BSC PF	Both groups PD	
CT scan	0.33	0.21	0.28	£111.98	£37.02	£23.70	£30.89	IMAG, weighted mean of all RD26Z codes
MRI scan	0.20	0.22	0.50	£150.77	£30.30	£33.50	£75.38	IMAG, weighted mean of all MRI – adult; codes: RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z.
FBC	0.63	0.37	0.45	£2.56	£1.60	£0.94	£1.16	DAPS, code DAPS05 – Haematology
LFT	0.63	0.36	0.43	£1.20	£0.75	£0.43	£0.51	DAPS, code DAPS04 - Clinical Biochemistry
Outpatient appointment	0.65	0.51	0.58	£200.20	£129.16	£101.36	£116.06	CL, Consultant led non-admitted face-to-face, follow-up; service code 370; currency code WF01A
Total cost	-	-	-	-	**£198.83**	**£159.93**	**£224.00**	**-**

BSC - best supportive care; PF - progression-free; PD - progressed disease; CT - computerised tomography; MRI - magnetic resonance imaging; FBC - full blood count; LFT - liver function test

Table 23: Pre-treatment costs (applied once only in first model cycle)

Item	Proportion of patients		Unit cost	Expected cost		NHS Reference Costs codes
	Ripretinib	BSC		Ripretinib	BSC	
CT scan	0.85	0.24	£111.98	£95.19	£26.88	IMAG, weighted mean of all RD26Z codes
MRI scan	0.12	0.01	£150.77	£18.09	£1.51	IMAG, weighted mean of all MRI adult; codes: RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z.
FBC	0.92	0.56	£2.56	£2.35	£1.43	DAPS, code DAPS05 – Haematology
LFT	0.92	0.49	£1.20	£1.10	£0.59	DAPS, code DAPS04 - Clinical Biochemistry
Total cost	-	-	-	**£116.73**	**£30.40**	**-**

BSC - best supportive care; CT - computerised tomography; MRI - magnetic resonance imaging; FBC - full blood count; LFT - liver function test

Table 24: Palliative treatment costs (applied once to all patients in the first model cycle and again at disease progression)

Item	Resource use per 28-days (both groups)	Unit cost	Expected cost (both groups)	NHS Reference Costs codes
Palliative resection	0.10	£3,893.52	£389.35	Total HRGs, Malignant gastrointestinal tract disorders with single intervention (weighted mean; codes FD11D, FD11E and FD11F)
Palliative RT	0.20	£182.87	£36.57	Total HRGs, Palliative care; weighted mean of SD01A, SD02A, SD03A, SD04A
Total cost	-	-	**£425.93**	-

BSC - best supportive care; RT – radiotherapy; HRG - Healthcare Resource Group

Table 25: Costs of managing AEs (applied once only in the first model cycle)

AE	AE frequency		Unit cost	Expected cost		NHS Reference Costs codes
	Ripretinib	BSC		Ripretinib	BSC	
Anaemia	0.11	0.14	£762.29	£80.80	£106.72	Total HRGs, weighted mean of SA01G:SA01K, SA03G:SA03H, SA04G:SA04L and SA05G:SA05J.
Abdominal pain	0.07	0.05	£649.11	£46.09	£30.51	Total HRGs, weighted mean of abdominal pain with interventions (FD05A) and without interventions (FD05B).
Hypertension	0.07	0.00	£638.81	£45.36	£0.00	Total HRGs, Hypertension (EB04Z)
Total cost	-	-	-	**£172.25**	**£137.23**	-

AE - adverse event; BSC - best supportive care; HRG - Healthcare Resource Group

End of life care costs

The costs of end of life care were taken from Abel *et al.*[32] The proportions of people dying in hospital or elsewhere and the costs of death by location reported in the paper were used to generate a weighted cost of death (see Table 26). The reported costs were uplifted to current values using Hospital and Community Health Service (HCHS) indices and NHS Cost Inflation Indices (NHSCII).[33, 34] The weighted cost of end of life care is applied to the number of new patients dying in each model cycle.

Table 26: End of life care costs

Place of death	Proportion of patients	Cost
Death in hospital	0.16	£13,099.67
Death elsewhere	0.84	£8,961.89
Weighted cost	-	**£9,634.90**

5.2.5 Model evaluation methods

The CS[1] presents base case cost-effectiveness results for ripretinib versus BSC using the using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 10,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are also presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). The distributions used in the company's PSA are summarised in Table 27.

The CS[1] presents the results of the deterministic sensitivity analyses (DSAs) graphically using a tornado plot and in tabular form. The CS also reports on a number of scenario analyses exploring alternative assumptions regarding: discount rates; the model time horizon; the distributions used to model PFS and OS; the method used to adjust OS for switching in the BSC group; the adjustment of OS in the ripretinib to account for continued treatment beyond disease progression; BSC costs; end of life care costs and the health state utility values.

Table 27: Summary of distributions used in company's PSA

Parameter/ group	Distribution applied in PSA	ERG comments
Patient characteristics		
Age	Fixed	It is unclear why sex is treated as uncertain, but age is not. This is a minor issue.
Probability male	Beta	
Time-to-event parameters		
PFS	Multivariate normal	-
OS	Multivariate normal	
TTD	Assumed to be equivalent to PFS	TTD sampling approach is reasonable given company's assumption of equivalence in outcomes.
HRQoL parameters		
Health state utility values	Beta	Does not account for ordered nature of data; hence, sampling allows utility values for PD to be higher than PF in the same PSA iteration.
AE QALY loss	Beta	Total QALY loss sampled assuming arbitrary SE of 20% of mean value. Underlying AE frequency not sampled.
Resource use and cost parameters		
Ripretinib acquisition costs	Fixed	-
Ripretinib RDI	Beta	-
Ripretinib compliance	Beta	-
BSC pain management costs	Gamma	Arbitrarily assumes SE is equal to 20% of the mean.
Pre-treatment costs	Gamma	Arbitrarily assumes SE is equal to 20% of the mean.
Health state costs	Gamma	Arbitrarily assumes SE is equal to 20% of the mean. Underlying use of individual resource components and unit costs are not sampled.
Palliative treatment costs	Gamma	Arbitrarily assumes SE is equal to 20% of the mean.
AE management costs	Gamma	Arbitrarily assumes SE is equal to 20% of the mean. Underlying AE frequencies are not sampled.
End of life costs	Gamma	Arbitrarily assumes SE is equal to 20% of the mean.

ERG - Evidence Review Group; PFS - progression-free survival; OS - overall survival; TTD - time to treatment discontinuation; AE - adverse event; QALY - quality-adjusted life year; PF - progression-free; PD - progressed disease; BSC - best supportive care; RDI - relative dose intensity; SE - standard error

5.2.6 Company's model results

Table 28 presents the central estimates of cost-effectiveness generated using the company's original submitted model. All results include the agreed PAS for ripretinib. The probabilistic version of the model suggests that ripretinib is expected to generate an additional [redacted] discounted QALYs at an additional cost of [redacted]; the corresponding ICER is £49,610 per QALY gained. The deterministic version of the model results in a slightly lower ICER of £49,441 per QALY gained.

Table 28: Company's base case results – ripretinib versus BSC, including ripretinib PAS

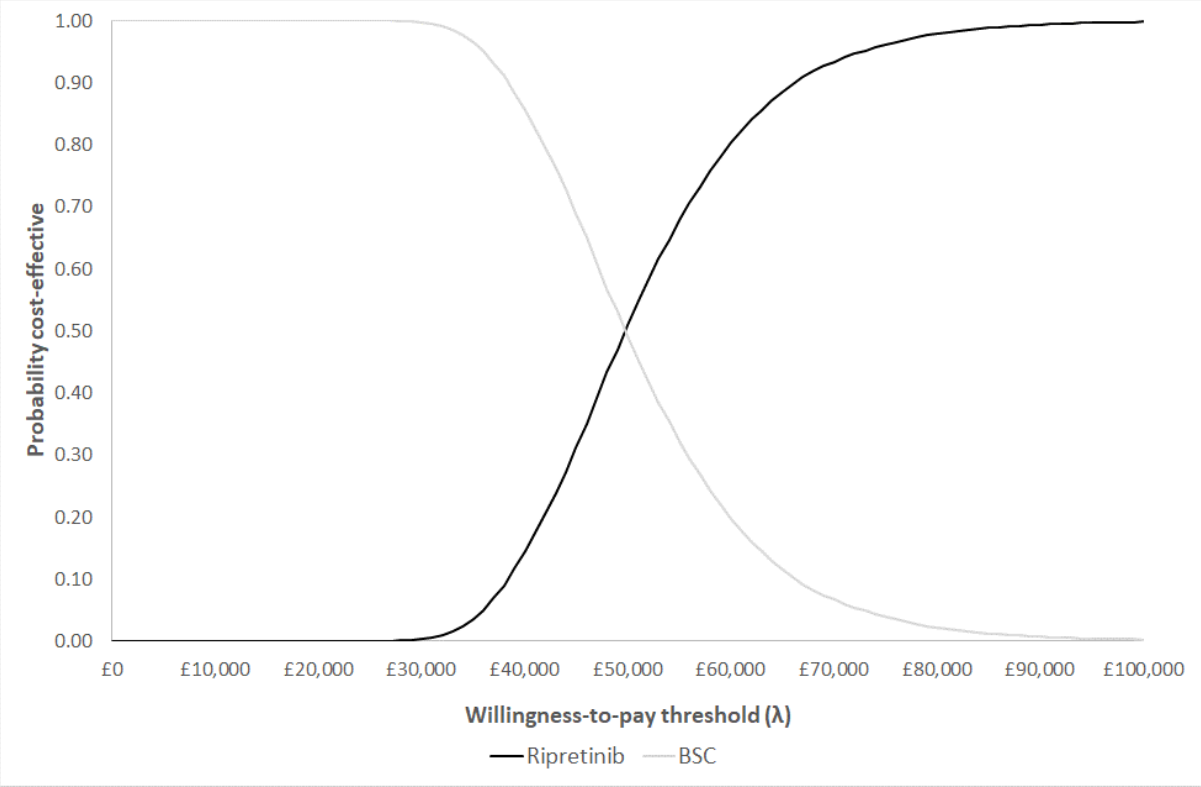
Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,610**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Deterministic model							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,441**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Undiscounted*
† Mean undiscounted LYGs generated by the ERG by modifying the company's VBA PSA sub-routine

Company's PSA results

The results of the company's PSA are presented as CEACs for ripretinib versus BSC in Figure 14. Assuming willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained, the probability that ripretinib generates more net benefit than BSC is expected to be approximately zero and 0.51, respectively.

Figure 14: Cost-effectiveness acceptability curves, ripretinib versus BSC, including ripretinib PAS (redrawn by the ERG)

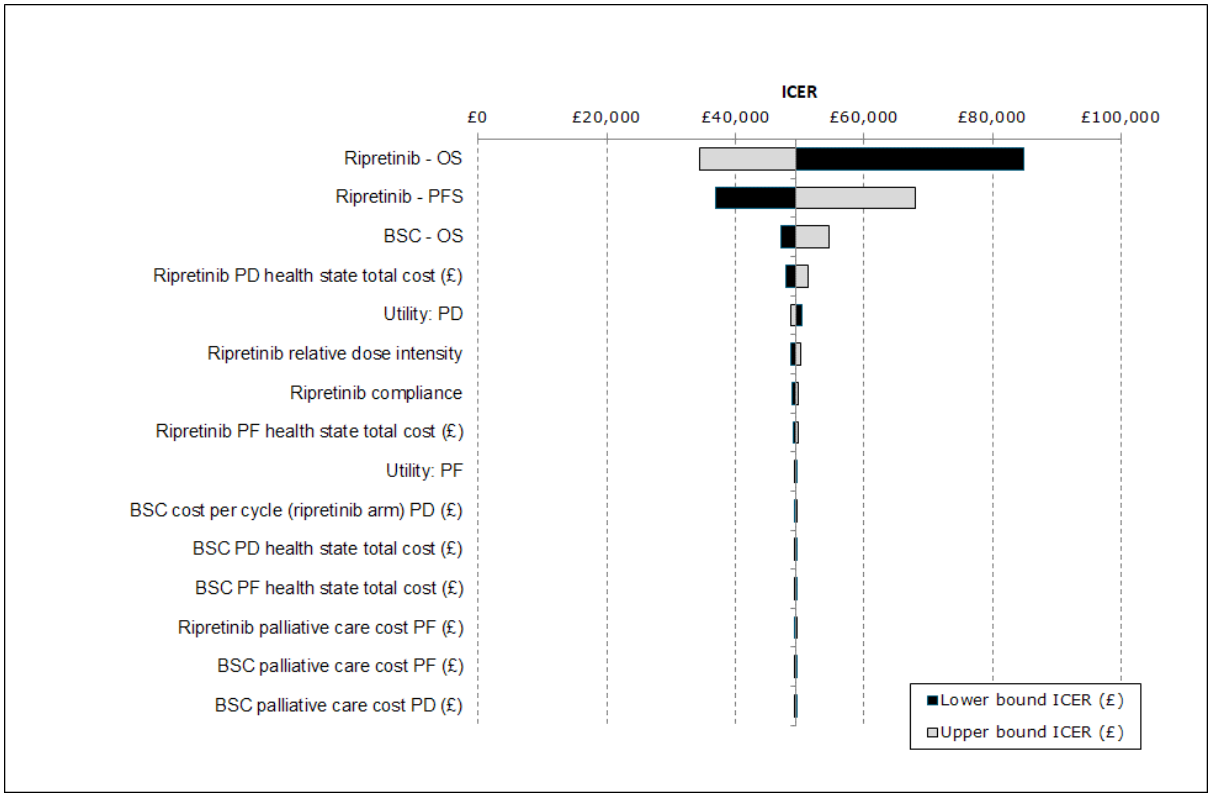


BSC - best supportive care

Company's DSA results

Figure 15 presents the results of the company's DSAs using a tornado plot. The plot indicates that the ICER is particularly sensitive to modelled PFS and OS in the ripretinib group. The lowest ICER generated within the DSAs is estimated to be £34,418 per QALY gained (ripretinib OS upper bound).

Figure 15: Company's tornado plot, ripretinib versus BSC, including ripretinib PAS (generated by the ERG)



ICER - incremental cost-effectiveness ratio; PFS - progression-free survival; OS - overall survival; PF - progression-free; PD - progressed disease; BSC - best supportive care

Company's scenario analysis results

Table 29 presents the results of the company's scenario analyses. As shown in the table, the ICER is substantially higher in the analysis in which OS for the ripretinib group is adjusted to account for potential confounding associated with continued treatment beyond disease progression (Scenario S16: ICER=£93,739 per QALY gained). The scenario analyses also indicate that the ICER increases when a greater difference is assumed between the utility values for the progression-free and progressed disease health states (Scenario S19: ICER=£54,641 per QALY gained). The ICER is also fairly sensitive to discount rates and the time horizon; however, the ERG does not consider these analyses to be particularly meaningful for informing decision-making as they do not adhere to the NICE Reference Case.

Table 29: Company's scenario analysis results – ripretinib versus BSC, deterministic, including ripretinib PAS

Scenario	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case (deterministic)	[redacted]	[redacted]	[redacted]	£49,441
S1. Discount rate = 0%	[redacted]	[redacted]	[redacted]	£41,291
S2. Discount rate = 1.5%	[redacted]	[redacted]	[redacted]	£44,901
S3. Discount rate = 6%	[redacted]	[redacted]	[redacted]	£54,704
S4. Time horizon = 10 years	[redacted]	[redacted]	[redacted]	£56,881
S5. Time horizon = 20 years	[redacted]	[redacted]	[redacted]	£50,886
S6. Time horizon = 30 years	[redacted]	[redacted]	[redacted]	£49,572
S7. PFS – log-logistic	[redacted]	[redacted]	[redacted]	£53,970
S8. PFS – generalised gamma	[redacted]	[redacted]	[redacted]	£47,681
S9. OS – log-logistic	[redacted]	[redacted]	[redacted]	£50,971
S10. OS – Gompertz	[redacted]	[redacted]	[redacted]	£47,394
S11. Placebo switching – complex 2-stage method without re-censoring	[redacted]	[redacted]	[redacted]	£51,086
S12. Placebo switching – complex 2-stage method with re-censoring	[redacted]	[redacted]	[redacted]	£50,717
S13. Placebo switching – simple 2-stage method without re-censoring	[redacted]	[redacted]	[redacted]	£49,360
S14. Placebo switching – RPSFTM with re-censoring	[redacted]	[redacted]	[redacted]	£50,035
S15. Placebo switching – RPSFTM without re-censoring	[redacted]	[redacted]	[redacted]	£50,595
S16. Ripretinib continued use adjustment – simple 2-stage method with re-censoring	[redacted]	[redacted]	[redacted]	£93,739
S17. End of life costs from Round *et al.*[37]	[redacted]	[redacted]	[redacted]	£49,441
S18. BSC costs from INVICTUS trial[5]	[redacted]	[redacted]	[redacted]	£50,627
S19. TA488[28] utility values (PF=0.767, PD=0.647)	[redacted]	[redacted]	[redacted]	£54,641

** Undiscounted*

S - scenario; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PFS - progression-free survival; OS - overall survival; RPSFTM - rank-preserving structural failure time model; BSC - best supportive care; TA - Technology Appraisal; PF - progression-free; PD - progressed disease

5.3 Critical appraisal

5.3.1 Critical appraisal methods

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying health economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[38, 39]
- Scrutiny and discussion of the company's model by the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.

- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2 Model verification by the ERG

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. As shown in Table 30, the ERG's results are virtually identical to those generated using the company's original submitted model. During the process of rebuilding the model, the ERG identified a number of minor programming errors; these are described in detail in Section 5.3.5, critical appraisal point [1]. The correction of these errors forms part of the ERG's exploratory analyses.

Table 30: Comparison of results from company's model and ERG's double-programmed model (excluding the correction of errors identified by the ERG)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Company's deterministic model							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,441.82**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG's double-programmed model							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,440.81**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Undiscounted*

5.3.3 Correspondence of the model inputs and the original sources of parameter values

Where possible, the ERG checked the company's model input values against their original sources. The ERG was able to identify the baseline age, sex, RDI, compliance and unit cost values from the CSR and/or the CS.[1, 5] The majority of other model parameters, including the survival model parameters and health state utility values, were generated from analyses of IPD from INVICTUS.[5] These data were not made available to the ERG; hence, the ERG is unable to verify that the analyses have been undertaken appropriately.

The ERG notes three potential issues regarding the input values used in the company's model:

(i) As noted in Section 5.2.4, the ERG was unable to identify the disutility value for anaemia or to determine how this value was derived from Harrow *et al.*[26] and Hoyle *et al.*[36] The ERG notes that this disutility value is not a key model driver.

(ii) The company's description of the derivation of the cost of treating anaemia (CS,[1] Table 37) includes Healthcare Resource Group (HRG) codes SA01G:SA01K, SA03G:SA03H, SA04H:SA04L and SA05G:SA05J. However, the weighted cost used in the model (£762.29) also includes HRG SA04G. The ERG assumes that the inclusion of this cost was intentional and that its exclusion from Table 37 of the CS is a minor typographical error.

(iii) The ERG was able to identify estimates of the frequency of tests and scans per model cycle from the physician survey described in the TA488 committee papers.[28] The company's model assumes that these frequencies apply to all patients. However, it appears that in TA488, these frequencies were combined with estimates of the proportion of patients who would undergo these tests, with the remainder not incurring these costs. This may reflect a minor error in the company's model.

5.3.4 Adherence to NICE Reference Case

The extent to which the company's economic model adheres to the NICE Reference Case[40] is summarised in Table 31. Overall, the ERG believes that the company's model is generally in line with the Reference Case. The most pertinent deviation relates to the absence of any economic comparison of fourth-line ripretinib versus continued regorafenib after progression (on third-line treatment), which the ERG's clinical advisors suggested would reflect usual practice for many patients. This issue is discussed further in Section 5.3.5, critical appraisal point [2].

Table 31: Adherence to the NICE Reference Case

Element of HTA	Reference Case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is partly in line with the final NICE scope.[3] However, the model compares ripretinib versus BSC, whilst the ERG's clinical advisors commented that many patients may continue to receive regorafenib following disease progression. No comparison has been presented between ripretinib versus the continued use of post-progression regorafenib.
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model includes health outcomes accrued by patients. Health impacts on caregivers are not included.
Perspective on costs	NHS and PSS	
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model includes a 40-year (lifetime) horizon. At the end of the time horizon, virtually all (>99.95%) patients in both treatment groups have died.
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are modelled based on data collected in the INVICTUS trial.[5] This is the pivotal Phase 3 trial of ripretinib for GIST. The study was identified within the company's SLR of clinical effectiveness studies.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health state utility values are based on EQ-5D-5L data collected in INVICTUS (mapped to the 3L version). Disutilities associated with AEs have been taken from external studies,[26, 27, 36] none of which are based on the EQ-5D instrument. These disutility values are applied for short duration and are not key model drivers.
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	QALY weighting is not included. The CS argues that ripretinib meets NICE's End of Life criteria.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The model includes costs borne by the NHS and PSS. Costs are taken from NHS Reference Costs,[31] the PSSRU,[34] the BNF[29] and relevant literature.[32]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5%.

HTA - health technology assessment; ERG - Evidence Review Group; NICE - National Institute for Health and Care Excellence; NHS - National Health Service; PSS - Personal Social Services; GIST - gastrointestinal stromal tumour; EQ-5D-5L - Euroqol 5-Dimensions (5-level); AE - adverse event; SLR - systematic literature review; ICER - incremental cost-effectiveness ratio; PSSRU - Personal Social Services Research Unit; BNF - British National Formulary

5.3.5 Main issues identified from the ERG's critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified during critical appraisal

(1) Model errors
(2) Absence of economic comparison against post-progression regorafenib
(3) Mismatch between anticipated positioning of ripretinib and evidence from INVICTUS
(4) Concerns regarding company's survival analysis methods
(5) Assumption that continued use of ripretinib in INVICTUS has not influenced post-progression survival
(6) Concerns regarding utility values
(7) Concerns regarding resource use and cost parameters
(8) Weak characterisation of uncertainty

(1) Model errors

The ERG's double-programming exercise revealed a number of minor errors in the company's original submitted model. These are summarised below:

(i) *Selection of life tables.* The company's model uses ONS life tables for the UK.[24] The ERG believes that it would be more appropriate to use life tables for England.

(ii) *Sex distribution applied in general population mortality risk.* The company's general population mortality risk calculations assume that: (a) men and women have different risks of death each year, and that (b) the proportion of men and women alive remains constant in every cycle. Both assumptions cannot simultaneously be true. The ERG believes that it would be more appropriate to estimate general population mortality risk using survival models for men and women weighted by their respective proportions at baseline in INVICTUS.[5]

(iii) *Incorrect age applied in general population mortality risk calculations.* The general population mortality risk calculations include an error which returns the risk for a population aged x+1 year, rather than age x.

(iv) *Incorrect logical applied in general population mortality risk constraint.* The formulae used to apply the generate general population mortality constraint determine whether the risk of death with the disease is greater than or equal to the risk of death in the age- and sex-matched general population in each given cycle. If the condition is met, the value returned is the cumulative survival probability from the unadjusted OS survival function. The ERG believes that if the condition is met, the adjusted cumulative probability of OS should be calculated as the probability of being alive at the end of the previous cycle multiplied by one minus the maximum death risk for the current cycle (death with the disease vs. death in the general population). In

principle, the company's approach can allow the cumulative OS function to increase between successive cycles.

(v) *Absence of any constraint for PFS.* No constraint has been to PFS – this means that the model can allow the cumulative probability of PFS to be higher than that for OS. This is logically inconsistent.

(vi) *Incorrect half-cycle correction*. The half-cycle correction calculations include an error whereby the first model cycle is counted 1.5 times.

(vii) *Inconsistent discounting approach*. The discount rate multipliers in each cycle are rounded down to the nearest integer value in the first year, but are not rounded down in subsequent cycles. This is inconsistent. The ERG also notes that LYGs presented in the model and the CS[1] are discounted, which is not informative.

(viii) *Inconsistent handling of time*. The model assumes that there are exactly 52 weeks per year; however, there are approximately 52.17 weeks per year.

(ix) *Missing brackets in health state cost calculations*. The formulae used to calculate discounted health state costs are missing a set of brackets which means that only part of the health state cost is discounted.

(x) *End of life care costs not discounted.* The formulae used to calculate end of life costs are not discounted.

(xi) *Inappropriate inclusion of treatment compliance as well as RDI.* RDI already accounts for non-compliance; hence, including both RDI and compliance parameters will underestimate the ripretinib drug acquisition costs (see critical appraisal point [7]).

As part of their clarification response,[2] the company submitted a revised version of the economic model which attempted to address most of the issues described above. The company's revised model suggested an ICER of £49,171 per QALY gained; this is slightly lower than the company's original base case ICER of £49,441 per QALY gained. However, the ERG notes the following issues regarding the updated model:

- *Issue (ii) – life tables*. The weighted general population survival model was incorrectly implemented, as the baseline male:female ratio was applied in every cycle, rather than only in the first cycle.
- *Issue (v) – PFS constraint.* The constraint was incorrectly implemented. If the cumulative probability of OS is lower than that for PFS in any cycle, the constrained cumulative PFS probability drops to zero for all subsequent cycles.
- *Issue (vi) – half-cycle correction.* The company's clarification response[2] (question B18) states that this issue has not been addressed and suggests that deleting the first row of the calculations

would be incorrect. The ERG notes that given the company's modelling approach, the health state occupancies in the first cycle should be halved, not removed. As such, the error remains.

- *Issue (vii) – discounting.* The discounting approach has been made consistent across all cycles, with discounting multipliers being down to the integer value of the year. However, a new error has been introduced whereby discounting is included in the undiscounted LYG estimates from the progressed disease state in the BSC group.
- *Issue (viii) – handling time.* The cycle length has been amended. However, some inconsistencies in how time units are defined are still evident (e.g., the number of cycles in one year is still 13 rather than 13.04). In addition, the survival models are estimated according to a cycle length of exactly 28 days.

Owing to these issues, the results of the company's revised model are not presented in detail here. Where possible, these issues detailed above have been addressed in the ERG's exploratory analyses (see Section 5.4).

(2) Absence of economic comparison against post-progression regorafenib

The company's economic model includes BSC as the sole comparator. The comparator listed in the final NICE scope[3] is defined as *"established clinical management without ripretinib including best supportive care."* The ERG's clinical advisors commented that in current practice in England, many patients (50% or more) who have progressed on regorafenib (after previously failing earlier treatment with both sunitinib and imatinib) would continue to receive this drug if they are benefiting from it, unless their disease is progressing rapidly or they are experiencing significant toxicity, and if no other treatments are available. Patients who do not receive regorafenib post-progression would receive BSC alone. The CS[1] does not provide an economic comparison of fourth-line ripretinib versus continued post-progression regorafenib; hence, the clinical effectiveness and cost-effectiveness of ripretinib against this comparator is unknown.

During the clarification round, the ERG asked the company to comment on the extent to which the placebo (plus BSC) comparator arm in the INVICTUS trial reflects current clinical practice and to provide an economic comparison of ripretinib versus continued post-progression regorafenib (see clarification response,[2] questions A2, A3 and C5, respectively). The company's clarification response states that clinical input was sought from a UK clinician, who stated that *"the availability of ripretinib in fourth line treatment for GIST would not affect their decision making regarding stopping treatment with regorafenib in third line"* and that *"treatment would generally be stopped if clear/aggressive progression occurred. However, in a minority of cases, if a patient's radiological progression is limited, and they continue to tolerate the therapy, then treatment may continue while the patient continued to have clinical benefit, only in absence of an alternative treatment option."* On the basis of their

clarification response, the company appears to be suggesting that few patients currently continue regorafenib post-progression and that if ripretinib did receive a positive NICE recommendation, this use of regorafenib would remain unchanged. However, the clarification response also suggests that patients progressing on regorafenib would only continue to receive it after progression if no other treatment was available (i.e., if ripretinib was not recommended). The ERG's clinical advisors stated that if ripretinib received a positive NICE recommendation, they would switch patients onto this ripretinib as soon as they have progressed on regorafenib. Overall, this would imply that continued post-progression regorafenib is a relevant comparator for ripretinib. The company has not provided this comparison. The ERG believes that it is unlikely that reliable evidence exists which would permit an ITC between fourth-line ripretinib versus continued post-progression regorafenib.

(3) Mismatch between anticipated positioning of ripretinib and evidence from INVICTUS

The company's intended positioning of ripretinib is after three prior lines of therapy, including imatinib (i.e., at fourth-line, see Figure 2). This is in line with the SmPC for ripretinib.[4] However, the INVICTUS trial[5] recruited patients who had received at least three prior therapies, rather than exactly three prior therapies. In INVICTUS, 48 of 129 patients (37.21%) had received between 4 and 7 prior lines of therapy (see Table 6). The ERG's clinical advisors commented that they would expect the number of prior therapies to be prognostic of outcomes, with PFS being potentially longer for patients who have received fewer lines of prior treatment. However, the clinical advisors also commented that patients who had reached seventh- or eighth-line therapy in INVICTUS may have a comparatively better disease biology than patients with fewer prior lines of therapy. The evidence from INVICTUS which is used to inform time-to-event outcomes in the economic model does not directly align with the company's intended positioning of ripretinib. Whilst it would be possible to restrict the trial data used in the model only to include those patients who have received exactly three prior treatments, this would result in a small sample size, particularly for the placebo group, and may introduce confounding as the number of lines of prior therapy was not a trial stratification factor. The overall impact of the mismatch between the trial population and the company's intended positioning on the cost-effectiveness of ripretinib is unclear.

During the clarification round, the ERG asked the company to comment on the extent to which the number of prior therapies for GIST might be prognostic of outcomes (see clarification response,[2] question A7). The company's response states that there was no statistically significant difference in relative treatment effects on PFS, OS and ORR for patients with 3 prior therapies versus 4 or more prior therapies in INVICTUS (although the ERG notes that the company has not formally tested this, but has instead erroneously inferred it on the basis of overlapping 95% CIs, which is incorrect[41]). The response also states that clinical input obtained by the company suggested that *"the benefit of ripretinib compared to placebo seen in INVICTUS was seen in fourth line patients as well as later line patients."* The

company's response also comments that *"it is unlikely that number of prior therapies is prognostic of outcomes."* The ERG notes that the company's clarification response focuses almost entirely on whether the number of prior treatment lines is a treatment effect modifier, rather than a prognostic factor. As such, it remains unclear whether the outcomes seen in the fourth- and later-line population in INVICTUS would be seen in the fourth-line population in NHS practice.

(4) Concerns regarding company's survival analysis methods

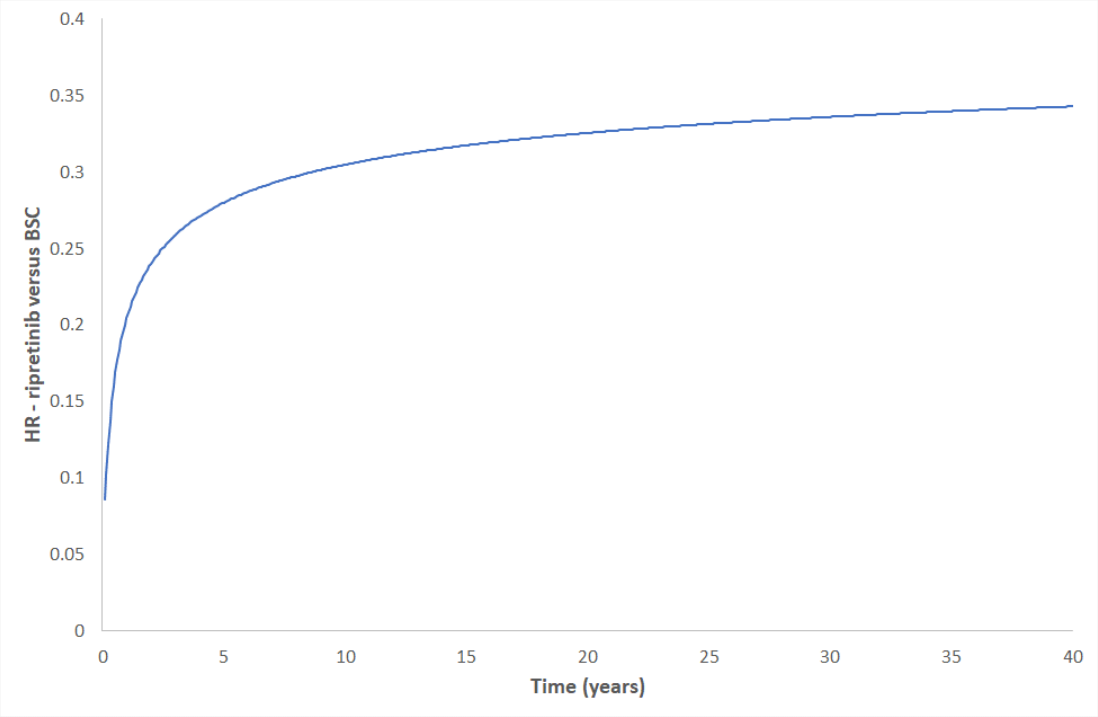
The ERG has several concerns regarding the parametric survival modelling presented in the CS.[1] These concerns are discussed below in terms of the general considerations around model fitting and selection set out in NICE DSU TSDs 14 and 21.[42, 43]

(a) Use of independent models fitted to data for each treatment group

The company considered the potential for jointly fitted models for PFS and OS through consideration of log cumulative hazard plots, plots of Schoenfeld residuals and global Schoenfeld residuals tests. For PFS, the CS[1] states that the log-cumulative hazards were not strictly parallel, the Schoenfeld residuals plot suggests that the HR is likely to vary over time and the global Schoenfeld test suggested a *p*-value which was less than 0.05. This indicates that the PH assumption may not hold. For OS, the CS comments that the log-cumulative hazard plot and Schoenfeld residuals plot suggest that applying the PH assumption would be reasonable and the global Schoenfeld test suggests that the PH assumption cannot be ruled out ($p>0.05$). However, the company instead elected to fit separate parametric survival models to the OS data for each treatment group (including adjustment of OS data to account for confounding due to switching in the placebo group).

The ERG notes that the plots and tests undertaken by the company relate specifically to the assessment of PH models (the exponential, Weibull and Gompertz distributions). Accelerated failure time (AFT) models do not make the PH assumption; the appropriateness of using jointly fitted models instead requires consideration of quantile-quantile (Q-Q) plots,[42] which have not been presented in the CS.[1] In general, the ERG prefers to avoid models which apply a constant HR or acceleration factor (AF), as this usually reflects an unnecessary and restrictive modelling assumption. As such, the ERG agrees with the company's decision to fit independent models to the data for each treatment group. However, the ERG also notes that whilst a constant lifetime treatment effect parameter (e.g., an HR or AF) is not used in the economic model, it is important to consider what is implicitly being assumed about relative treatment effects for ripretinib versus BSC. Figure 16 shows that the independent log-normal OS models implicitly suggest a time-varying HR for OS which favours ripretinib over BSC at all timepoints (i.e., the HR is consistently <1.0). Given that almost all ripretinib-treated patients are estimated to have progressed or died after 3 years (see Figure 11), and patients are assumed to discontinue ripretinib at the point of disease progression, this is likely to reflect a highly optimistic assumption.

Figure 16: Time-varying HR for OS implied by independent log-normal models used in the company's base case analysis*



BSC - best supportive care
** HR calculated from approximate hazard for in each group*

(b) Range of models assessed

The company fitted six standard parametric models to the available data on PFS and OS (see Figure 11 and Figure 12). Other more flexible survival distributions, e.g., RCS models, were not considered. The ERG notes that, based on visual assessment alone, some of the fitted standard models appear to provide a good fit to the PFS data in both groups. However, the overall visual fit of the models to the ripretinib OS data is poor, and the Kaplan-Meier function suggests that there may be potential turning points in the underlying hazard function. The use of more flexible parametric models may have been better able to reflect the observed data.

(c) Statistical and visual goodness-of-fit

The company appears to have selected models largely on the basis of statistical goodness-of-fit. The ERG notes the following observations regarding the fitted models:

- *PFS (see Figure 11 and Table 17):* The log-logistic model has the lowest combined AIC and BIC values across both treatment groups. The log-normal model provides similar combined AIC and BIC values, and the generalised gamma model provides a similar fit in terms of combined AIC, but not BIC. The company selected the log-normal distribution for inclusion in the economic model. All six fitted models appear to give similar projections for the BSC group. With respect to the ripretinib group, the log-logistic and log-normal models have longer tails and provide more optimistic extrapolations compared with the other candidate models. These

two models both appear to overestimate PFS compared with the observed data after around 1.5 years.

- *OS (see Figure 12 and Table 18).* The log-logistic model has the lowest combined AIC value, whereas the exponential model has the lowest combined BIC value. The log-normal model provides a similar fit in terms of combined AIC and BIC values. The company selected the log-normal distribution for inclusion in the economic model. Visually, all models provide broadly similar projections of OS for the BSC group, with very few patients surviving beyond 2 years. Within the ripretinib group, the log-logistic, log-normal, Gompertz and generalised gamma models provide much more optimistic extrapolations compared with the Weibull and exponential models. All of the models for the ripretinib group appear to overestimate OS relative to the observed data after around one year.

Given the apparent absence of consideration of other model selection criteria (e.g., the nature of the empirical hazard and modelled hazard functions and/or clinical plausibility), the company's justification for not selecting the best-fitting model for both PFS and OS is not fully clear.

(d) Consideration of nature of hazards

The CS[1] does not present plots of the empirical and/or modelled hazard functions for any of the time-to-event endpoints. These plots can be useful for assessing whether the hazard functions for the selected models are consistent with the underlying empirical hazards in the observed data.

Following a request for additional analysis by the ERG, the company provided plots of the empirical and modelled hazards for PFS and OS (see clarification response,[2] question C3). The hazard plots for PFS for the ripretinib and BSC groups are reproduced in Figure 17 and Figure 18, respectively. The hazard plots for OS for the ripretinib and BSC groups are reproduced in Figure 19 and Figure 20, respectively. The company subsequently clarified that the OS hazard plot shown in Figure 20 includes adjustment for treatment switching in the placebo group, whilst the plot shown in Figure 19 reflects the unadjusted ripretinib OS data (as per the company's base case analysis).

Figure 17: Unsmoothed, smoothed, and modelled hazards – ripretinib PFS (reproduced from clarification response, question C3)

Gen gamma - generalised gamma

Figure 18: Unsmoothed, smoothed, and modelled hazards – BSC PFS (reproduced from clarification response, question C3)

BSC - best supportive care; Gen gamma - generalised gamma

Figure 19: Unsmoothed, smoothed, and modelled hazards – ripretinib OS (corrected version provided by company after receipt of clarification response)

Gen gamma - generalised gamma

Figure 20: Unsmoothed, smoothed, and modelled hazards – BSC OS (reproduced from clarification response, question C3)

BSC - best supportive care; Gen gamma - generalised gamma

With respect to these hazard plots, the ERG makes the following observations:

- The smoothed hazard for PFS in both treatment groups appears to increase, decrease and then increase again (see Figure 17 and Figure 18). The log-normal distribution, which was selected for inclusion in the company's base case analysis, assumes that the hazard increases and then

decreases. The company's clarification response notes that only 8 patients in the placebo group remain at risk after 8 weeks; hence, the plot should be interpreted with caution. Notwithstanding this uncertainty, the modelled hazard for the log-normal distribution appears to be inconsistent with the empirical hazard for PFS in both groups. However, none of the fitted parametric survival models reflect this underlying pattern. It is possible that more flexible parametric models could have better reflected the empirical hazard.

- The smoothed hazard for OS in both treatment groups appears to increase and then decrease (see Figure 19 and Figure 20). This is generally consistent with the underlying assumptions of the log-normal model which was selected for inclusion in the company's base case analysis. The ERG notes that the empirical hazard in both groups decreases much more rapidly than the hazards from the company's log-normal models.
- The empirical hazard of OS for the ripretinib group, including adjustment for post-progression ripretinib use, has not been presented by the company.

(e) Consideration of long-term clinical plausibility

The CS[1] (page 57) states that *"The best-fitting curves were selected based on statistical fit and clinical plausibility."* However, the model selection process described in the CS refers only to the use of AIC and BIC statistics and visual inspection to inform model selection. The CS does not provide any information the use of clinical input to inform parametric model selection or to assess the plausibility of the final model predictions of PFS and OS.

The ERG asked their clinical advisors for their views regarding the plausibility of the company's model predictions of PFS and OS. Their views are summarised below:

PFS

- Both clinical advisors considered the company's predictions of PFS based on the log-normal distributions (the dashed and solid red lines in Figure 11), to be plausible for both treatment groups. One advisor commented that it was plausible that all patients receiving BSC would progress within one year and that a small proportion of patients receiving ripretinib could derive a longer-term benefit in PFS.

OS

- Both clinical advisors commented that they believed that continuing ripretinib beyond disease progression would lead to additional OS benefits.
- The ERG's first clinical advisor stated that model-predicted OS for the BSC group, based on the log-normal distribution (the dashed red line in Figure 12), was *"very reasonable"* as they would expect 85-90% of patients to have died within 1 year, and a small proportion of patients who have lower volume progressive disease may survive for longer on BSC alone. However, the clinical

advisor did not consider the company's model-predicted OS for the ripretinib group based on the log-normal distribution (the solid red line in Figure 12) to be plausible. In particular, they commented that they would not expect 10% of patients to still be alive 10 years after starting fourth-line treatment with ripretinib and that survival out to this timepoint is not realistic even for patients receiving other TKIs (imatinib, sunitinib or regorafenib) at earlier lines of treatment. They also commented that whilst the exponential and Weibull models (the solid orange and blue lines in Figure 12) suggest comparatively lower OS than the log-normal model, these are also likely to be optimistic. The clinical advisor commented that given that virtually all patients in the ripretinib arm of INVICTUS[5] are known to have progressed by 2 years, they would expect that only around 10-20% of patients would still be alive at 3 years, despite the use of post-progression ripretinib. The clinical advisor further commented that they would not expect a residual treatment effect on OS in patients after they have discontinued ripretinib. Overall, none of the company's fitted models are consistent with the clinical advisor's expectations of OS for ripretinib. Following the clarification round, the ERG's clinical advisor suggested that if ripretinib was discontinued at disease progression, they would expect OS to be around 6 months longer than PFS.

- The ERG's second clinical advisor provided broadly similar views to the first clinical advisor. With respect to the BSC group, they stated that in this patient population, it is likely that nearly all patients will have died within 1.5 years. They commented that for the BSC group, the log-normal distribution (the dashed red line in Figure 12) might be overly optimistic, whilst the Weibull and Gompertz models (the dashed grey and orange lines in Figure 12) appear overly pessimistic. Their preferred model would be between these two survival functions. With respect to the ripretinib group, the clinical advisor also commented that the company's selected log-normal model (the solid red line in Figure 12) appears to be optimistic for fourth-line treatment and that the exponential and Weibull models (the solid blue and orange lines in Figure 12) reflect *"a more plausible situation."* However, they also commented that their preference for the exponential/Weibull model only reflects a situation whereby ripretinib is continued after disease progression. If ripretinib was stopped in all patients at the point of disease progression, they would expect a sharper decline in the ripretinib OS function. They agreed with the first clinical advisor's expectation that OS would be around 6 months longer than PFS if treatment is stopped at progression.

(f) Sensitivity analysis

The CS[1] presents the results of a limited set of scenario analyses which consider the use of the log-logistic and generalised gamma models for PFS and the use of the log-logistic and Gompertz models for OS (see Table 29). Other models are not explored in the CS.

ERG's conclusions regarding company's survival modelling

Overall, the ERG considers the company's survival modelling to be limited, in particular due to: (i) the poor visual fit of the selected log-normal models to the ripretinib OS data; (ii) the absence of consideration of hazard functions and clinical plausibility in the model selection process; (iii) the implicit assumption of a lifetime treatment effect on OS despite the assumption of a progression-based stopping rule and (iv) the implausibly optimistic extrapolation of OS in the ripretinib group.

(5) Assumption that continued use of ripretinib post-progression in INVICTUS has not influenced post-progression survival

As discussed in Section 5.2.4, patients in both treatment arms in the INVICTUS trial[5] could receive ripretinib following disease progression. Patients who progressed whilst on placebo could switch to receive ripretinib (150mg QD). The company present the results of several methods to adjust for this switching (Section B.3.3 and Table 45 of the CS[1] and clarification response,[2] question B4). Results of these switching analyses are generally robust to the choice of method and the ERG is satisfied with the approach taken here. Patients who progressed whilst receiving ripretinib could continue to receive ripretinib at either the same dose (150mg QD) or an increased dose (150mg BID). This contrasts with the company's stopping rule which assumes that ripretinib is not used after progression. In their base case analysis, the company assumes that this continued use of ripretinib post-progression has no impact on the resulting estimates of OS – in other words, the model assumes that the same outcomes observed in INVICTUS could be achieved simply by using less of the drug. This is in direct contrast with clinical advice to the ERG and the results of the company's analyses that account for continued use, which both suggest that continued ripretinib use post-progression would be expected to improve subsequent OS. In addition, in response to clarification question B9,[2] the company suggested that post-progression utility values observed in the INVICTUS trial were increased by continued use of ripretinib (as discussed further in the following sub-section). This post-progression utility benefit, along with the high rates of continued ripretinib use post-progression (at least 49% of patients in the ripretinib group) both lend further credence to the hypothesis that continued ripretinib use confers a benefit to subsequent OS. Hence, the ERG believes that an appropriate base case analysis which includes the company's proposed stopping rule would include an adjustment of OS to account for the impact of continued ripretinib use after disease progression. When adjusting for treatment switching from the placebo arm, the company provided the methodology for and results of six approaches (three methods: simple two-stage, complex two-stage, RPSFTM). Less evidence was provided when adjusting for continued ripretinib use post-progression (see clarification response,[2] question B5). For example, there was no discussion of the suitability of the RPSFTM approach, or of the impact of re-censoring. As such, it is unclear which OS adjustment method should be considered the most appropriate in the ripretinib group. Despite this uncertainty, any method that is used to adjust OS in the ripretinib group would shrink the OS estimate for ripretinib and would lead to an ICER which is higher than the company's base case estimate.

(6) Concerns regarding utility values

The ERG has concerns regarding the appropriateness of the health state utility values applied in the company's model (utility progression-free = [redacted]; utility progressed disease = [redacted]). These estimates were based on EQ-5D-5L values measured in INVICTUS[5] (mapped to the 3L version). In particular, the utility value for the progressed disease state is very similar to that applied in the progression-free health state (a difference of [redacted], which is applied for the entire remaining survival period after progression). The ERG considers that this value is unlikely to fully reflect average HRQoL over patients' entire post-progression survival time, as the final EQ-5D-5L assessments were measured [redacted].[5] The ERG is also unclear why patients who were censored for progression were removed from the dataset used to estimate the utility values (see Section 5.2.4), as this could result in selection bias and informative censoring. In addition, as ripretinib was received after progression in both groups of INVICTUS, this is likely to have resulted in higher utility values than would be seen in patients with progression receiving BSC alone. No adjustment has been made to attempt to adjust for the impact of post-progression ripretinib use on the utility values estimated from the trial.

Table 28 of the CS[1] provides a summary of heath state utility values identified from the company's SLR; an adapted version of this table is shown in Table 32. Most of these utility values are based on analyses of the A6181004 trial[44] and the GRID trial.[22] With the exception of Zolic *et al.,*[45] which reports particularly high utility values with and without disease progression, the utility value for progressed disease after four or more lines of treatment from INVICTUS[5] is considerably higher than all other estimates of post-progression utility after fewer lines of prior therapy.

The ERG's clinical advisors commented that whilst patients are still receiving treatment, they are generally able to maintain a relatively good level of HRQoL, but that when they discontinue treatment, HRQoL deteriorates rapidly, in particular, due to the greater impact of disease symptoms. The advisors considered that the utility value for the progression-free state from INVICTUS was higher than what would be expected in a typical patient receiving fourth-line treatment and that the utility value applied in the progressed disease state is implausibly high. The advisors also commented that there would likely be a difference in HRQoL between those patients who are progression-free and on ripretinib and those who have progressed but are still obtaining clinical benefit, with the former being higher than the latter.

Table 32: Summary of health state utility values identified from company's review of HRQoL studies (adapted from CS, Table 28)

Reference	Population	Method of elicitation/valuation	PF utility	PD utility
First-line GIST				
Wilson *et al.* (2005)[46]	Unresectable and/or metastatic GIST	ECOG PS category (from CST157I-B2222 trial[47]) mapped to EQ-5D by 3 clinicians	0.935	0.875
Second-line GIST				
NICE TA179(sunitinib)[48]	Advanced GIST; resistant to or intolerant of previous treatment with imatinib	EQ-5D measured in RCT (Study A6181004[44])	Sunitinib 0.731 BSC 0.781	0.577
Paz-Ares *et al.* (2008)[49]			Sunitinib 0.712 BSC 0.781	0.577
Chabot *et al.* (2008)[50]			Sunitinib 0.712 BSC 0.781	0.577
Hislop *et al.* (2011)[51]		PF utility taken from Wilson *et al.*[46] (ECOG PS mapped to EQ-5D). PD utility based on Chabot *et al.*[50] (EQ-5D measured in RCT).	0.935	0.52
Third-line GIST				
PBAC (regorafenib)[52]	Unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib	EQ-5D measured in RCT (GRID trial[22])	0.767	0.647
SMC (regorafenib)[53]			0.74	0.68
Zolic *et al.* (2015)[45]			Paired samples 0.872 Repeated measures model 0.850	Paired samples 0.806 Repeated measures model 0.814
Poole *et al.* (2015)[23]			Baseline 0.76 Paired samples 0.707	Paired samples 0.647
Liao *et al.* (2021)[21]			0.767	0.647
Rui *et al.* (2021)[54]			Pazopanib 0.780 Regorafenib 0.779	0.647
Fourth- and subsequent-line GIST				
Company's model[1]	Advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modification after 3 or more prior therapies	EQ-5D measured in RCT (INVICTUS trial[5])	[redacted]	[redacted]

GIST - gastrointestinal stromal tumour; PF - progression-free; PD - progressed disease; ECOG - Eastern Cooperative Oncology Group; PS - performance status; EQ-5D - Euroqol 5-Dimensions; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; RCT - randomised controlled trial

The company's clarification response[2] (question B9) provides further analyses of EQ-5D data collected in INVICTUS. The additional analyses include a breakdown of mean EQ-5D values by treatment group and cycle, and mean EQ-5D values by treatment group, whether patients are on or off treatment and progression status. The latter analysis is reproduced in Table 33.

Table 33: EQ-5D-3L utility values by treatment group, treatment status and progression status (adapted from clarification response, question B9)

Treatment group	Treatment status (number of observations)	Mean utility value	
		Progression-free	Progressed disease
Ripretinib	On treatment (N=)		
	Off treatment (N=)		
BSC	On treatment (N=)		
	Off treatment (N=)		
All patients	On treatment (N=)		
	Off treatment (N=)		

BSC - best supportive care; N - number

The company's clarification response notes that the following:

- The high utility value for the progressed disease state can be attributed to the high proportion of BSC group patients who received ripretinib post-progression.
- Patients who continued to receive ripretinib following progression will have experienced a further gain in HRQoL.
- The company suggests that informative censoring is possible, but is unlikely to have affected post-progression estimates. The ERG notes that the numbers of observations for patients who are off-treatment are much smaller compared with patients who remain on treatment.

The ERG generally agrees with the company's likely explanations for the post-progression high utility value estimated from INVICTUS.[5] Given that the company's proposed use of ripretinib is only up to the point of disease progression, whilst INVICTUS permitted ripretinib to be used post-progression in both treatment groups, the ERG does not consider the INVICTUS ITT dataset to be an appropriate source for the utility value in the progressed disease state. Rather, the ERG believes that it may be more appropriate to use the mean utility value for patients with progressed disease who are not receiving treatment in INVICTUS (progressed disease utility =) or an estimate from the literature which is broadly consistent with the characteristics of the target population (for example, the GRID trial progressed disease utility = 0.647).

The ERG also notes that the company's original model did not include any age-adjustment of health state utility values. This was included in the company's updated model provided post-clarification and is included in the ERG's exploratory analyses (see Section 5.3.5).

(7) Concerns regarding resource use and cost parameters

The ERG believes that there are two problems relating to the cost parameters used in the company's model. These relate to: (a) the inclusion of both compliance and RDI estimates in the drug acquisition cost calculations and (b) the assumption of zero drug wastage costs for ripretinib.

(a) Inclusion of both RDI and compliance

The company's model includes both RDI and compliance. These parameters lower the net drug acquisition costs for ripretinib. According to the CSR for INVICTUS,[5] compliance was calculated as the total number of days dosed divided by the treatment duration in days multiplied by 100. RDI was calculated as the total dose (mg) divided by the total planned dose (mg) multiplied by 100. The ERG believes that the RDI estimate already reflects the average amount of the planned dose received, and therefore already accounts for any effect of non-compliance. Therefore, including both of these parameters in the model will lead to the ripretinib acquisition costs being underestimated. The ERG raised this concern with the company during the clarification round. In their clarification response[2] (question B11), the company agreed that this is a problem; this issue is corrected in the ERG's exploratory analyses (see Section 5.4).

(b) Exclusion of drug wastage costs

The company's model calculates drug acquisition costs based on the amount of drug required per day, based on an implicit assumption that packs can be split. This approach assumes zero wastage, as only tablets which are taken are costed in the model. In reality, patients who progress or die before finishing a pack of ripretinib will incur some drug wastage costs.

During the clarification round, the ERG asked the company to comment on whether they had intentionally omitted drug wastage from the model (see clarification response,[2] question B12). The company's response states *"Ripretinib is an orally administered tablet, therefore it would not be appropriate to apply wastage in the model, as any tablets not taken would be captured within RDI."* The ERG disagrees that RDI is likely to account for wastage incurred by patients who do not finish a full pack of ripretinib due to progression or death; therefore, wastage costs should be included in the model. In line with previous appraisals, the ERG believes that it would be reasonable to assume that, on average, each patient treated with ripretinib would waste one quarter of a pack. The ERG's clinical advisors considered this assumption to be reasonable.

(8) Weak characterisation of uncertainty

As noted in Table 27, for the majority of model's cost parameters, the company has arbitrarily assumed that the SE is equal to 20% of the mean value, even in instances in which the published sources include sufficient information to estimate the SE of the sample. It is unclear why this approach has been adopted.

The ERG also notes that independent beta distributions have been used to draw samples of health state utility values; this approach ignores the ordered nature of the data and allows for utility values for people with progressed disease to be higher (better) than the utility for people who are progression-free. As a consequence of these two issues, the results of the company's PSA are unlikely to adequately reflect decision uncertainty.

5.4 Exploratory analyses undertaken by the ERG

5.4.1 ERG exploratory analysis - methods

The ERG undertook exploratory analyses (EAs) using the original version of the company's model. The ERG's preferred analysis is comprised of four sets of amendments. All EAs were undertaken using the deterministic version of the model. Probabilistic analyses were undertaken; however, some of these are subject to problems which limits their usefulness (see Section 5.4.2). All analyses were implemented by one modeller and checked by a second modeller.

All analyses presented in this section reflect the PAS price of ripretinib and the list prices of drugs included in BSC. The results of the analyses including Commercial Medicines Unit (CMU) price discounts for BSC drugs are presented in a separate confidential appendix to this report.

5.4.1.1 ERG's preferred analysis

The ERG's preferred analysis is comprised of four separate sets of amendments to the company's original model.

EA1: Correction of errors

The ERG applied the following corrections to the company's updated model:

- General population mortality risk for patients at each age was re-estimated using a weighted survival model based on life tables for England.[55]
- The formulae used to estimate adjusted OS including the general population mortality constraint were modified to apply the highest per-cycle risk of death with the disease or from the life tables
- A constraint was added to ensure that the cumulative probability of PFS is capped by the cumulative probability of OS at every time point
- A half-cycle correction was applied to the model trace
- The discounting formulae were applied without rounding down to integer values. All discounting was removed from the LYGs calculations.
- Brackets were added to the health state cost calculations to ensure that all components of the formulae are discounted.
- Discounting was included for end of life care costs.
- Ripretinib compliance was set equal to 1.00.

The ERG was unable to fully resolve the inconsistencies regarding the handling of time (see Section 5.3.5, critical appraisal point [1], issue [viii]), as this would require multiple changes throughout the whole model structure. The ERG believes that resolving these issues would likely have a minimal impact on the ICER.

Details regarding the implementation of EA1 within the executable model can be found in Appendix 1. All subsequent exploratory analyses include these model corrections.

EA2: Inclusion of OS adjustment in ripretinib group and use of generalised gamma model

The model was amended to: (a) include the adjustment of OS data for the ripretinib group to account for the effect of continued post-progression ripretinib use and (b) apply the generalised gamma OS model fitted to these adjusted OS data. The generalised gamma model was selected because the ERG's clinical advisors commented that if ripretinib was stopped on progression, they would expect OS to be around 6 months longer than PFS and this model was consistent with the ERG's clinical advisors' expectations (see Table 34 and Figure 21). These amendments were applied using existing drop-down menus in the company's model. The ERG's clinical advisors noted that the Weibull model also provides potentially plausible OS predictions for the adjusted ripretinib group; alternative OS models fitted to the adjusted OS data were explored in the ERG's additional sensitivity analyses (see Section 5.4.1.2).

Table 34: Mean time in progression-free and progressed disease states based on company's selected PFS model and alternative OS models (includes switching adjustment in both placebo and ripretinib groups)*

OS model	Ripretinib			BSC		
	Time in PF state (years)	Time in PD state (years)	Total OS (years)	Time in PF state (years)	Time in PD state (years)	Total OS (years)
Exponential	[redacted]					
Weibull						
Gompertz						
Log-normal						
Log-logistic						
Generalised gamma						

BSC - best supportive care; OS - overall survival; PF - progression-free; PD - progressed disease; OS - overall survival
** Calculated using half-cycle corrected trace from ERG corrected model*

Figure 21: Comparison of ERG's and company's preferred OS models for the ripretinib group

ERG - Evidence Review Group; OS - overall; survival; BSC - best supportive care; gen. gamma - generalised gamma

EA3: Utility value for progressed disease state based on GRID trial

The utility value for the progressed disease state was assumed to be 0.647, based on the GRID trial.[23] The ERG notes that this estimate is very similar to the utility value for patients with progressed disease who were off-treatment in INVICTUS[5] (utility = [redacted]). The ERG's preferred analysis retains the company's utility value for the progression-free health state (utility = [redacted]). Age-adjustment of utility values was also included using a multiplicative approach based on EQ-5D-3L estimates for the UK reported Hernandez Alava *et al.*[56]

EA4: Inclusion of drug wastage assumptions

The model was amended to assume that all patients incur wastage equivalent to one quarter of a pack of ripretinib.

EA5: ERG preferred analysis

The ERG's preferred analysis includes all amendments included in EAs 1-4.

5.4.1.2 ERG's additional sensitivity analyses

Three sets of additional sensitivity analyses (ASAs) were undertaken using the ERG's preferred model.

ASA1: Alternative PFS models

The model was re-run using all six standard parametric survival models fitted to the PFS data from INVICTUS.[5]

ASA2: Alternative OS models

The model was re-run using all six standard parametric survival models fitted to the OS data from INVICTUS,[5] including adjustment for switching in the placebo group and continued post-progression treatment in the ripretinib group.

ASA3: Wastage set equal to half a pack

The model was amended to assume that, on average, each patient wastes half of pack of ripretinib.

5.4.2 ERG exploratory analysis – results

Table 35 presents the results of the ERG's preferred analysis for the comparison of ripretinib versus BSC. The ERG's analyses indicate that the correction of errors reduces the company's base case ICER from £49,441 to £44,667 per QALY gained (EA1). Including adjustment of the ripretinib OS data to account for continued treatment after progression and selecting the generalised gamma model for OS increases the ERG's error-corrected ICER to £124,504 per QALY gained (EA2). Applying a utility value of 0.647 to the progressed disease state and including age-adjustment of all utility values increases the ERG's error-corrected ICER to £50,818 per QALY gained (EA3). Including additional wastage costs increase the ERG's error-corrected ICER to £45,747 per QALY gained (EA4). The deterministic version of the ERG's preferred model (EA5), which combines all of these amendments suggests that the ICER for ripretinib versus BSC is £134,241 per QALY gained. The main driver of this higher ICER is the use of a less optimistic OS model fitted to the adjusted OS data for the ripretinib group.

Table 35: ERG's preferred analysis results, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,441**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA1: Correction of errors							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,677
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA2: Inclusion of OS adjustment in ripretinib group and use of generalised gamma model							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£124,504
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA3: Utility value for progressed disease state based on GRID trial plus age-adjusted utility values							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,818
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA4: Inclusion of drug wastage assumptions							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,747
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
EA5: ERG preferred analysis							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£134,241**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; EA - exploratory analysis; OS - overall survival; ERG - Evidence Review Group

Table 36 presents the results of the ERG's additional sensitivity analyses. The results indicate that the ERG's preferred model is not particularly sensitive to the selected PFS model (ASA1), or to the inclusion of higher wastage costs (ASA3). The model is sensitive to the choice of OS model; however, the lowest ICER across all scenarios remains in excess of £96,000 per QALY gained.

Table 36: ERG's additional sensitivity analysis results, deterministic

Scenario no.	Scenario description	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
EA5	**ERG preferred analysis**	[redacted]	[redacted]	[redacted]	**£134,241**
ASA1a	PFS = exponential	[redacted]	[redacted]	[redacted]	£128,872
ASA1b	PFS = Weibull	[redacted]	[redacted]	[redacted]	£127,363
ASA1c	PFS = Gompertz	[redacted]	[redacted]	[redacted]	£128,568
ASA1d	PFS = log-logistic	[redacted]	[redacted]	[redacted]	£137,665
ASA1e	PFS = generalised gamma	[redacted]	[redacted]	[redacted]	£131,244
ASA2a	OS = exponential	[redacted]	[redacted]	[redacted]	£115,722
ASA2b	OS = Weibull	[redacted]	[redacted]	[redacted]	£137,032
ASA2c	OS = Gompertz	[redacted]	[redacted]	[redacted]	£144,316
ASA2d	OS = log-normal	[redacted]	[redacted]	[redacted]	£96,316
ASA2e	OS = log-logistic	[redacted]	[redacted]	[redacted]	£100,315
ASA3	Wastage = 0.5 packs	[redacted]	[redacted]	[redacted]	£137,633

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ASA - additional sensitivity analysis; PFS - progression-free survival; OS - overall survival
**Note – all analyses include OS adjustment in both treatment groups*

Probabilistic model results

The ERG re-ran ASA2 (all OS models) using the probabilistic version of the model. The mean LYGs, QALYs, costs and ICERs when applying the exponential, Weibull, log-normal and log-logistic OS models estimated using the probabilistic model were very similar to those obtained from the deterministic version of the model. However, the probabilistic ICERs generated using the Gompertz and generalised gamma models were both considerably lower than the deterministic ICERs (Gompertz ICER: £61,877 versus £144,316 per QALY gained; generalised gamma ICER: £113,512 versus £134,241 per QALY gained). These discrepancies appear to be a consequence of issues in the probabilistic sampling of the OS model parameters, which subsequently impacts on expected QALYs and costs for ripretinib and BSC. For the Gompertz OS distribution, the multivariate normal sampling routine appears to have been implemented appropriately, but sampled parameter values frequently include negative values – these lead to sampled OS extrapolations whereby all patients remain alive for some period of time and then all die instantly. For the generalised gamma model, the reason for the discrepancy is less obvious, although the ERG notes that in many probabilistic iterations, the sampled OS distribution has a very long tail, which leads to the expected time spent alive with progressed disease to be much longer than the estimate generated from the deterministic version of the model (0.86 years versus 0.51 years). As such, the results of the PSA using the generalised gamma are inconsistent with the ERG's clinical advisors' views on expected OS. Usually, the ERG would suggest that probabilistic analyses should be used to inform decision-making. However, given the inconsistency in OS estimates between the deterministic and probabilistic versions of the model, the ERG believes that the results of the deterministic model are more appropriate in this instance.

5.5 Discussion

The CS[1] includes an SLR of existing economic studies of treatments for GIST and details the methods and results of a *de novo* model-based health economic analysis of ripretinib versus BSC in patients who have had at least three prior therapies for advanced or metastatic GIST.

The company's SLR identified one existing economic model of fourth- and subsequent-line ripretinib versus BSC (Liao *et al.*[21]), although the CS[1] states that no relevant studies were identified by the review. The ERG notes that this published analysis is limited, as it does not include statistical adjustment of OS for post-progression ripretinib use in either treatment group.

The company's economic model assesses the cost-effectiveness of ripretinib plus BSC versus BSC alone for the fourth- and subsequent-line treatment of patients with advanced GIST. The model adopts a partitioned survival approach which includes three health states: (i) progression-free; (ii) progressed disease and (iii) dead. The analysis adopts an NHS and PSS perspective, including QALYs accrued by GIST patients; caregiver effects are not included. Clinical outcomes for both groups are based on

parametric survival models fitted to data on PFS and OS from INVICTUS,[5] including adjustment of OS in the BSC group to account for treatment switching. The company's base case analysis assumes that ripretinib would be discontinued at progression, but does not include any adjustment of OS in the ripretinib group to account for post-progression ripretinib use in the trial. Health state utility values are based on data from INVICTUS (unadjusted for post-progression ripretinib use); resource use and cost parameters were taken from a clinical expert survey used in TA488[28] and standard costing sources[29, 31, 34] and other literature.[37]

The company's submitted model predicts that patients receiving ripretinib have a mean PFS of [redacted] years and a mean OS of [redacted] years, whereas patients receiving BSC alone have a mean PFS of [redacted] years and a mean OS of [redacted] years. The probabilistic version of the company's model suggests that the ICER for ripretinib versus BSC is £49,610 per QALY gained. The deterministic ICER is similar (£49,441 per QALY gained).

The ERG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's model. The ERG has five main concerns regarding the company's submitted economic model:

(i) The company's base case model does not include adjustment of OS to account for post-progression ripretinib use in the ripretinib arm of INVICTUS.[5] This assumes that treatment with ripretinib received after progression in the trial did not affect the observed survival outcomes (i.e., that the same outcomes observed in INVICTUS could be achieved by using less of the drug). The company's scenario analyses and the ERG's exploratory analyses indicate that adjusting OS in the ripretinib group using the two-stage method shrinks the OS in the ripretinib group and substantially increases the ICER for ripretinib versus BSC.

(ii) The ERG's clinical advisors did not consider the company's predicted OS for ripretinib ([redacted] years) to be plausible, particularly in the company's base case scenario whereby all patients discontinue ripretinib at disease progression. The ERG's clinical advisors suggested that OS for ripretinib is likely to be around 6 months longer than PFS.

(iii) The ERG's clinical advisors were concerned that the company's treatment stopping rule runs contrary to clinical recommendations on the use of TKIs in patients with active disease progression.[6, 8] The ERG's clinical advisors and the UK clinical advisor consulted by the company[2] indicated that they would want to use ripretinib beyond disease progression in patients that could still obtain benefit from continued treatment. No economic analysis has been presented without the proposed stopping rule. The ERG believes that such an analysis should have been considered.

(iv) In current practice, many patients who have progressed on third-line regorafenib continue to receive the drug after disease progression. The ERG asked the company to undertake an

economic comparison of fourth-line ripretinib versus continued regorafenib (after progression at third-line). The company's clarification response argues that regorafenib is not a relevant comparator and this economic analysis has not been provided.

(v) The EQ-5D data collected in INVICTUS[5] are likely to have been confounded by post-progression ripretinib use and therefore are unlikely to reflect the average level of HRQoL experienced by patients who have progressed on four or more therapies who are receiving BSC alone.

The ERG's critical appraisal also identified other less important issues, including several minor programming errors, limitations in the process used to select preferred survival models and the absence of age-adjustment of utility values. The ERG also notes that there is a mismatch between the evidence from INVICTUS, which included patients who had received at least three prior therapies, and the company's proposed positioning of ripretinib in patients who have received exactly three prior therapies; the implications of this on the economic model predictions are unclear.

The ERG's preferred model includes: (i) the correction of model errors (where possible); (ii) the use of generalised gamma models fitted to OS data which have been adjusted for post-progression ripretinib use in both treatment groups; (iii) the use of the post-progression utility value reported from the GRID trial[23] (including age-adjustment) and (iv) the inclusion of drug wastage costs. The ERG's preferred model suggests that the deterministic ICER for ripretinib versus BSC is £134,241 per QALY gained. The ERG's additional sensitivity analyses indicate that the ICER is fairly sensitive to the choice of OS model; however, based on survival models fitted to OS data which have been adjusted in both treatment groups, the ICER remains in excess of £96,000 per QALY gained in all scenarios. The ICER for ripretinib versus BSC is less sensitive to the choice of PFS model and wastage assumptions.

6. END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Section B.2.1.3 of the CS[1] argues that ripretinib meets NICE's EoL criteria. With respect to the short life expectancy criterion, the CS states patients in the placebo group of INVICTUS[5] had a median OS of 6.6 months; when OS was adjusted for treatment switching in the placebo group using the simple two-stage method, median OS was estimated to be [redacted] months. With respect to the life extension criterion, the CS states that the ITT analysis of INVICTUS suggests that ripretinib increases median OS by 8.5 months; when OS was adjusted for treatment switching in the placebo group using the simple two-stage method, the median OS gain for ripretinib versus BSC was estimated to be [redacted] months.

The ERG considers that the mean values represent a more appropriate measure of central tendency than medians, as the latter do not take account of the shape of the tail of the distribution. Table 37 summarises the mean undiscounted LYGs predicted by the company's base case model and the ERG's preferred model. As shown in the table, both the company's base case model and the ERG's preferred model suggest a very short OS for the BSC group. The ERG's preferred estimates of incremental OS are substantially less than those predicted by the company's base case model ([redacted] years versus [redacted] years). Nonetheless, the ERG agrees that ripretinib is very likely to meet NICE's EoL criteria.

Table 37: Mean estimates of undiscounted LYGs predicted by company's base case model and ERG's preferred model

	Company's base case model*	ERG's preferred model
OS adjustment for post-progression ripretinib use	BSC group only	Ripretinib and placebo groups
Preferred OS model (both groups)	Log-normal	Generalised gamma
Mean undiscounted LYGs in BSC group	[redacted]	[redacted]
Mean undiscounted LYGs in ripretinib group	[redacted]	[redacted]
Incremental LYGs	[redacted]	[redacted]

ERG - Evidence Review Group; OS - overall survival; LYG - life year gained; BSC - best supportive care
**Excludes correction of errors identified in ERG's critical appraisal*

7. OVERALL CONCLUSIONS

Clinical effectiveness conclusions

The CS presents data from the INVICTUS RCT of ripretinib plus BSC versus placebo plus BSC in 129 patients with advanced GIST who had progressed on, or were intolerant to, (at least) imatinib, sunitinib and regorafenib. The ERG's clinical advisors considered INVICTUS to be broadly representative of UK clinical practice. However, there were some differences between INVICTUS and the company's proposed use of ripretinib. The company's positioning of ripretinib is fourth-line, while more than one-third of patients in INVICTUS had >3 prior therapies. Whilst the company states that they are seeking a positive NICE recommendation for ripretinib up to the point of disease progression, in INVICTUS patients could receive ripretinib beyond progression, and the ERG's clinical advisors stated that they would want to be able to use ripretinib beyond progression.

As of the May 2019 data cut-off, 29 of 44 (66%) patients had crossed over to ripretinib and 42 of 85 (49%) patients had moved to open-label ripretinib after progression. At this data cut-off, median PFS was 6.3 months for ripretinib versus 1.0 months for placebo (HR 0.15, 95% CI 0.09 to 0.25, p<0.0001). Median OS was 15.1 months for ripretinib versus 6.6 months for placebo (HR 0.36, 95% CI 0.21 to 0.62, p=NR), 11.6 months in placebo crossover patients, and 1.8 months in placebo non-crossover patients. The most common TEAEs with ripretinib (vs. placebo) were alopecia (52% vs. 5%); fatigue (42% vs. 23%); nausea (39% vs. 12%); abdominal pain (37% vs. 30%); constipation (34% vs. 19%); myalgia (32% vs. 12%); diarrhoea (28% vs. 14%); decreased appetite (27% vs. 21%); PPES (21% vs. 0%) and vomiting (21% vs. 7%). TEAEs of special interest included SCC of the skin (2 [2.4%] vs. 0%) and actinic keratosis (5 [5.9%] vs. 1 [2.3%]).

Cost-effectiveness conclusions

The company's base case model provides an economic comparison of ripretinib versus BSC for patients with advanced GIST after at least three prior treatments. The company's economic model includes a stopping rule whereby ripretinib is assumed to be discontinued at the point of disease progression; however, the model does not include any adjustment of the OS data from INVICTUS to account for the effect of post-progression ripretinib use in the intervention group. The company's base case ICER is estimated to be £49,411 per QALY gained. The ERG's preferred model: (i) includes the correction of several model errors (ii) includes adjustment of the ripretinib group OS data to account for post-progression ripretinib use and applies an alternative (generalised gamma) OS model based on clinical judgement; (iii) applies a lower utility value for the progressed disease state and (iv) includes costs of drug wastage. The ERG's preferred model suggests a considerably higher ICER of £134,241 per QALY gained. The main driver of this higher ICER is the adjustment of the ripretinib group OS data.

The ERG's clinical advisors commented that many patients who progress on third-line regorafenib continue to receive regorafenib post-progression. The ERG believes that this should have been considered as a comparator. However, the company has not presented a comparison of fourth-line ripretinib versus continued post-progression regorafenib; it is unlikely that sufficient evidence exists to inform an ITC between these treatments.

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9. APPENDICES

Appendix 1: Description of corrections applied in ERG Exploratory Analysis 1

Number of patients

For easier interpretation, the number of patients has been set equal to 1. In worksheet "Settings" cell G15, the value has been replaced with "1"

Apply PAS

Worksheet "Data Store", cell D19 has been replaced with "[redacted]"

Set ripretinib compliance equal to 1.0

Worksheet "Cost Inputs", cell F14 has been replaced with "100%"

Clarification letter question B14, Issue (a) Inappropriate life tables

Life tables for England have been applied in worksheet "ERG_WeightedGenPopModel", cells C6:D106

Clarification letter question B14, Issue (b) Sex-weighted general population risks

A weighted survival model has been generated – see worksheet "ERG_WeightedGenPopModel", cells K6:O527

Clarification letter question B14, Issue (c) General population mortality risk applied at age x+1 rather than x

The formulae in worksheet "Clinical Inputs" cells C69:C589 have been linked to the per-cycle risks from the weighted general population survival model in worksheet "ERG_WeightedGenPopModel". Specifically, in worksheet "Clinical Inputs" cell C70 has been amended to "=ERG_WeightedGenPopModel!O10". This has been filled down to row 589.

Clarification letter question B14, Issue (d) Incorrect application of general population mortality constraint

In worksheet "Clinical Inputs", the formula in cell I70 has been amended to "=I69*(1-MAX(H70,C70))". This has been filled down to row 589. The formula in cell L70 has been amended to "=L69*(1-MAX(K70,C70))". This has been filled down to row 589.

Clarification letter question B14, Issue (e) Absence of a PFS constraint

In worksheet "Clinical Inputs", the formula in cell E69 has been amended to "=MIN(IF(AND($D$9="Yes",D69<$D$11),'KM Data'!E99,CHOOSE('Data Store'!$S$135,'Survival Analysis'!E63,'Survival Analysis'!F63,'Survival Analysis'!G63,'Survival Analysis'!H63,'Survival Analysis'!I63,'Survival Analysis'!J63)),I69)". This has been filled down to row 589.

The formula in cell F69 has been amended to "=MIN(IF(AND($D$9="Yes",D69<$D$12),'KM Data'!L99,CHOOSE('Data Store'!$U$135,'Survival Analysis'!$Y63,'Survival Analysis'!$Z63,'Survival Analysis'!$AA63,'Survival Analysis'!$AB63,'Survival Analysis'!$AC63,'Survival Analysis'!$AD63)),L69)". This has been filled down to row 589.

Clarification letter question B14, Issue (f) Incorrect application of half-cycle correction

Worksheet "Trace (Ripretinib)" cell I9 has been replaced with "=SUM(E9,E10)/2". This has been filled across to column K and down to row 528.

The formula in cell W9 has been amended to "=1*(Intervention_ae_cost_X)*1/(1+dr_cost)^$C9"

The formula in cell AQ9 has been amended to

"=(($I9*(util_healthstate1))/(cycles/time)*(1/(1+dr_outcomes)^$C9))-(Intervention_ae_disutility_X/13)"

The formula in cell M9 has been amended to

"=(I9*((Intervention_compliance*Intervention_RDI*Intervention_trt_cost_X)+(Comparator1_compliance*Comparator1_RDI*Intervention_BSC_cost_healthstate1))*1/(1+dr_cost)^$C9)+Int_pretrt_cost"

Worksheet "Trace (BSC)" cell I9 has been replaced with "=SUM(E9,10)/2". This has been filled across to column K and down to row 528.

The formula in cell W9 has been amended to "=1*(Comparator1_ae_cost_X)*1/(1+dr_cost)^$C9"

The formula in cell AQ9 has been amended to

"=(($I9*(util_healthstate1))/(cycles/time)*(1/(1+dr_outcomes)^$C9))-(Comparator1_ae_disutility_X/13)"

The formula in cell M9 has been amended to

"=(I9*((Comparator1_compliance*Comparator1_RDI*Comparator_trt_cost_healthstate1))*1/(1+dr_cost)^$C9)+Comparator_pretrt_cost"

In the traces for both treatment groups, the final row of the half-cycle corrected trace assumes that all patients have reached the death state (i.e., a value of "0" has been applied in cells I528:J528 and a value of "1.0" has been applied in cell K528).

Clarification letter question B14, Issue (g) Age inappropriately rounded down in year 1

Worksheet "Trace (Ripretinib)" cell C9 has been amended to "=D9*4/52". This has been filled down to row 528.

Worksheet "Trace (BSC)" cell C9 has been amended to "=D9*4/52". This has been filled down to row 528.

Clarification letter question B14 Issue, (h) LYGs discounted in the results sheet

Worksheet "Results" cell E10 has been amended to "=SUM('Trace (BSC)'!I9:J528)/13"

Worksheet "Results" cell E11 has been amended to "=SUM('Trace (Ripretinib)'!I9:J528)/13"

Clarification letter question B14, Issue (i) Rounding of time and cycles

This has not been amended as it permeates through most of the model. The impact of this issue is likely very minor.

Clarification letter question B14, Issue (j) Definition of time units in survival analysis

This has not been amended as the ERG did not have access to the IPD from INVICTUS. The impact of this issue is likely very minor.

Clarification letter question B14, Issue (k) Missing brackets from health state cost calculations

Worksheet "Trace (Ripretinib) " cell S10 has been amended to
"=(($J10*Intervention_HealthState2_cost_X)+((E9-
E10)*Intervention_palliative_cost))*(1/(1+dr_cost)^$C10)"
This has been filled down to row 528.
Worksheet "Trace (BSC)" cell S10 has been amended to
"=(($J10*Comparator1_HealthState2_cost_X)+((E9-
E10)*Comparator_palliative_cost))*(1/(1+dr_cost)^$C10)"
This has been filled down to row 528.
Note - the uncorrected trace has purposefully been used in the above calculations.

Clarification letter question B14, Issue (l) End of life care cost not discounted

Worksheet "Trace (Ripretinib)" cell AD10 has been amended to "=((G10-
G9)*EOL_cost)*(1/(1+dr_cost)^$C10)"
This has been filled down to row 528.
Worksheet "Trace (BSC)" cell AD10 has been amended to "=((G10-
G9)*EOL_cost)*(1/(1+dr_cost)^$C10)"
This has been filled down to row 528.
Note - the uncorrected trace has purposefully been used in the above calculations.

Clarification letter question B14, Issue (m) Utility values permit illogical ordering

This issue has not been amended as the ERG as the ERG has concerns regarding the reliability of the OS model predictions generated using the probabilistic model (see Section 5.4.2).

Implementing EA2-5 and ASA1-3

Other ERG exploratory analyses can be implemented using the drop-down menus in worksheet "Clinical Inputs" and by setting the flags in worksheet "ERG_AgeAdjustedUtilities&Waste" cells L2, L4 and L6 to 1.0 or 0.