NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Deciphera Pharmaceuticals**

2. **Clarification questions and company responses**
   a. Initial response
   b. Second response
   c. Third response

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. GIST Cancer UK
   b. Sarcoma UK

4. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Andrea Weston – Patient Expert, nominated by GIST Cancer UK
   b. Bradley Price, Policy and Public Affairs Manager, Sarcoma UK – Patient Expert, nominated by Sarcoma UK
   c. Dr Charlotte Benson, Consultant Medical Oncologist – Clinical Expert, nominated by Sarcoma UK
   d. Kate Jones-Cole – Patient Expert, nominated by GIST Cancer UK
   e. Dr Ramesh Bulusu, Consultant Oncologist and Network GIST Lead – Clinical Expert, nominated by GIST Cancer UK

8. **Technical engagement responses and statements from stakeholders:**
   a. GIST Cancer UK
   b. PAWS-GIST

9. **Evidence Review Group critique of company response to technical engagement** prepared by School of Health and Related Research (ScHARR)
   a. ERG critique
   b. ERG plots of modelled survival curves

Any information supplied to NICE which has been marked as confidential, has been

redacted. All personal information has also been redacted.

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Single technology appraisal

Gastrointestinal stromal tumours (advanced) – ripretinib (after 3 therapies) [ID3805]

Document B

Company evidence submission

May 2022

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Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
4L	Fourth-line
AE	Adverse event
AIC	Akaike information criterion
ANC	Absolute change in neutrophil count
BD	Twice a day
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice a day
BSC	Best supportive care
CAN	Canadian
CEM	Cost-effective model
CI	Confidence interval
CIUP	Continued imatinib until progression
CUA	Cost-utility analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ERG	Evidence Review Group
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IPE	Iterative parameter estimation
IPCW	Inverse Probability of Censoring Weights

ITT	Intent-to-treat
IU	International units
IV	Intravenous
KM	Kaplan-Meier
LY	Life year
LYG	Life year gained
m/r	Modified release
mRECIST v1.1	modified Response Evaluation Criteria in Solid Tumors version 1.1
NICE	National Institute for Health and Care Excellence
NR	Not recorded
OD	Once a day
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PbR	Payment-by-results
PD	Progressed disease
PF	Progression-free
PFLY	Progression-free life year
PFS	Progression-free survival
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
PSD	Public summary document
PSM	Partitioned survival models
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QC	Quality control
QD	Once a day
QDS	Four times a day
QoL	Quality of life
RCT	Randomised controlled trial

RPSFT	Rank preserving structural failure time
RPSFTM	Rank preserving structural failure time model
SD	Standard deviation
SE	Standard error
SGD	Singapore dollar
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SLR	Systematic literature review
SUS	Sistema Único de Saúde
STA	Single technology appraisal
TA	Technology appraisal
TDM	Therapeutic drug monitoring
TDS	Three times a day
TEAE	Treatment-emergent adverse event
TGT	Targeted gene therapy
UAPR	Upfront abdominoperineal resection
VEGFR-3	Vascular-endothelial growth factor-3
WHO	World Health Organisation

B.1 Decision problem, description of the technology and clinical care pathway

Advanced gastrointestinal stromal tumour (GIST) is a rare and highly complex disease with a number of mutations fuelling resistance and progression of disease. The standard treatment for patients in the UK with advanced GIST is imatinib followed by sunitinib then regorafenib. Patients will ultimately develop drug resistance to tyrosine kinase inhibitors (TKIs) and experience disease progression. There remains an unmet clinical need in the post-regorafenib setting due to the high rate of disease progression and recurrence that is linked with significant morbidity and mortality, and the lack of affordable and effective treatments.

Ripretinib has a dual mechanism of action that provides broad inhibition of KIT and PDGFRA kinase activity, including wild-type and multiple primary and secondary mutations associated with drug-resistant GIST in later lines of therapy (1,2).

Ripretinib is a novel switch-control TKI that broadly inhibits KIT and PDGFRA kinase signalling through a dual mechanism of action. Ripretinib is designed to bind both the switch pocket region and the activation switch to lock the kinase in this inactive state, preventing downstream signalling and cell proliferation (1,2).

Ripretinib has demonstrated an improvement in progression-free survival (mPFS of 6.3 months vs 1 month for placebo), significantly reducing the risk of disease progression or death by 85% (HR of 0.15 [95% CI: 0.09; 0.25]; p<0.0001) in the INVICTUS Phase 3 randomised controlled trial (3).

Ripretinib has also showed a clinically meaningful improvement over placebo in overall survival (OS) (median OS 15.1 months vs. 6.6 months, HR = 0.36), and showed similar results with 19 months of additional follow-up (median OS 18.2 months vs. 6.3 months, HR = 0.41) (3,4). Ripretinib was well-tolerated and demonstrated an acceptable safety profile.

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem that is addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 (1) – see appendix C
Intervention	Ripretinib	As per scope	N/A
Comparator(s)	Established clinical management without ripretinib including BSC	As per scope	N/A
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
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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the	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 (5,6). Therefore, no additional	N/A

	intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing in people with advanced GIST who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	diagnostic testing is expected.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Previous treatment with tyrosine kinase inhibitors whose disease has progressed • Resistance or intolerance to tyrosine kinase inhibitors	No subgroups considered	All patients of interest are resistant or intolerant or have progressed on tyrosine kinase inhibitors
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

Abbreviations: BSC – Best supportive care; GIST – Gastrointestinal stromal tumour; HRQoL – Health-related quality-of-life; N/A – Not applicable; NHS – National Health Service; NICE - National Institute for Health and Care Excellence; OS – Overall survival; PFS – Progression-free survival; SmPC – Summary of product characteristics.

B.1.2 Description of the technology being appraised

Table 2 presents a brief description of ripretinib for treating advanced GIST after 3 therapies. The Summary of product characteristics (SmPC) can be found in appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Ripretinib (Qinlock®).
Mechanism of action	Ripretinib is a novel tyrosine kinase inhibitor 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 (1).
Marketing authorisation/CE mark status	The EMA centralised procedure filing was on 14th September 2020. MHRA approved ripretinib on 21st December 2021 (7). CHMP gave a positive opinion on 16th September 2021 (8). Marketing authorisation was received on 18th November 2021 from the EMA (9).
Indications and any restriction(s) as described in the SmPC	Ripretinib is indicated for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib (1). Contraindications are hypersensitivity to the active substance or to any of the excipients listed in the SmPC (1).
Method of administration and dosage	Ripretinib is an oral therapy. The recommended dose is 150 mg ripretinib (three 50 mg tablets) taken once daily at the same time each day with or without food (1). If the patient misses a dose of ripretinib within 8 hours of the time it is usually taken, the patient should be instructed to take it as soon as possible and then take the next dose at the regularly scheduled time. If a patient misses a dose by more than 8 hours of the time it is usually taken, the patient should be instructed not to take the missed dose and simply resume the usual dosing schedule on the following day (1). In case of vomiting after ripretinib administration, the patient should not take a replacement dose and should resume the dosing schedule the next day at the usual time (1).

Table 2: Technology being appraised

	Treatment with ripretinib should continue as long as benefit is observed or until unacceptable toxicity. Dose interruptions or dose reductions may be required based on individual safety and tolerability. The recommended dose reduction for adverse reactions is 100mg orally, once daily (1).
Additional tests or investigations	Patients with or a history of high blood pressure will be monitored during ripretinib treatment and may administer medicine to treat high blood pressure, if needed (1). For patients with or a history of heart conditions, patients will have additional tests to assess heart function prior to and during ripretinib treatment (1). Ripretinib may increase the risk of some types of skin cancers. Patients' skin will be checked when starting ripretinib treatment and routinely during treatment (1).
List price and average cost of a course of treatment	£18,400 list price per 30-day supply, based on a dose of 150 mg once daily (3 x 50 mg tablets). As an oral treatment, ripretinib is VAT exempt.
Patient access scheme (if applicable)	A patient access scheme will be submitted in the form of a simple discount on the list price of ripretinib.

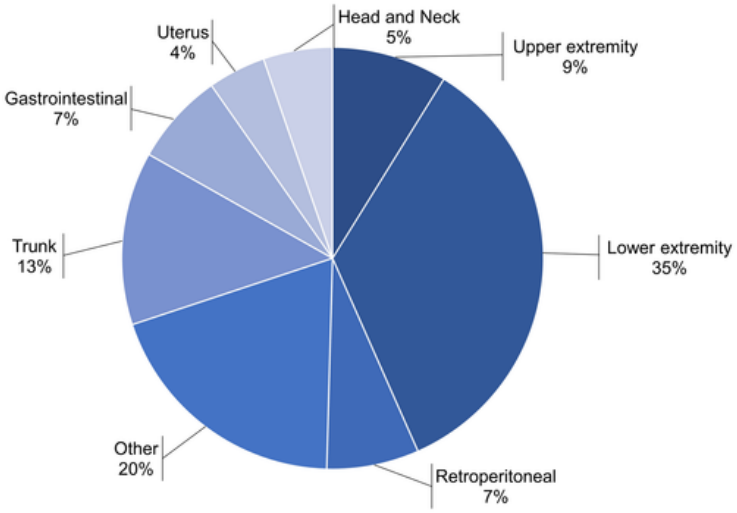
Abbreviations: CHMP – Committee for Medicinal Products for Human Use; EMA - European Medicines Agency; GIST – Gastrointestinal stromal tumour; MHRA – Medicines & Healthcare products Regulatory Agency; SmPC – Summary of product characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Soft tissue sarcoma (STS) represents a heterogeneous group of diseases that account for 1% of malignancies in adults (10). GISTs are a rare and heterogeneous subset of STS and are the most common mesenchymal tumour of the gastrointestinal (GI) tract (11,12). Approximately 7% of STS cases are GIST (Figure 1) (10).

Figure 1: Histologic subtypes of soft tissue sarcomas



Source: Gamboa et al. 2020 (10).

GIST develops in specialised interstitial cells of Cajal within the GI tract, driven by mutations in the KIT transmembrane receptor tyrosine kinase and the related receptor tyrosine kinase, PDGFRA (11,12). GIST may present as a malignant or benign tumour (13). Mutations in the genes encoding these receptors (*KIT/PDGFRA*) can lead to constitutively activated KIT or PDGFRA, which is a primary factor underlying the development of GIST (14).

Pathophysiology and molecular subtypes

The aetiology and underlying pathogenesis of GIST is not well-established (5,15). Prior to the development of specific diagnostic codes and immunohistochemical characterisation, GISTs were often misdiagnosed as smooth muscle, submucosal, and abdominal tumours up until the late 1990s. Since then, the diagnosis and reporting of GISTs have increased due to an increased disease awareness with the introduction of unique diagnostic codes (11,16). Current characterisation of GIST encompass previous diagnoses of smooth muscle tumours, such as leiomyomas, leiomyoblastomas, leiomyosarcomas and schwannomas; true GI smooth muscle tumours are rare outside of the oesophagus or colon (12,17).

GISTs have distinctive histologic features and present heterogeneously as (12,15):

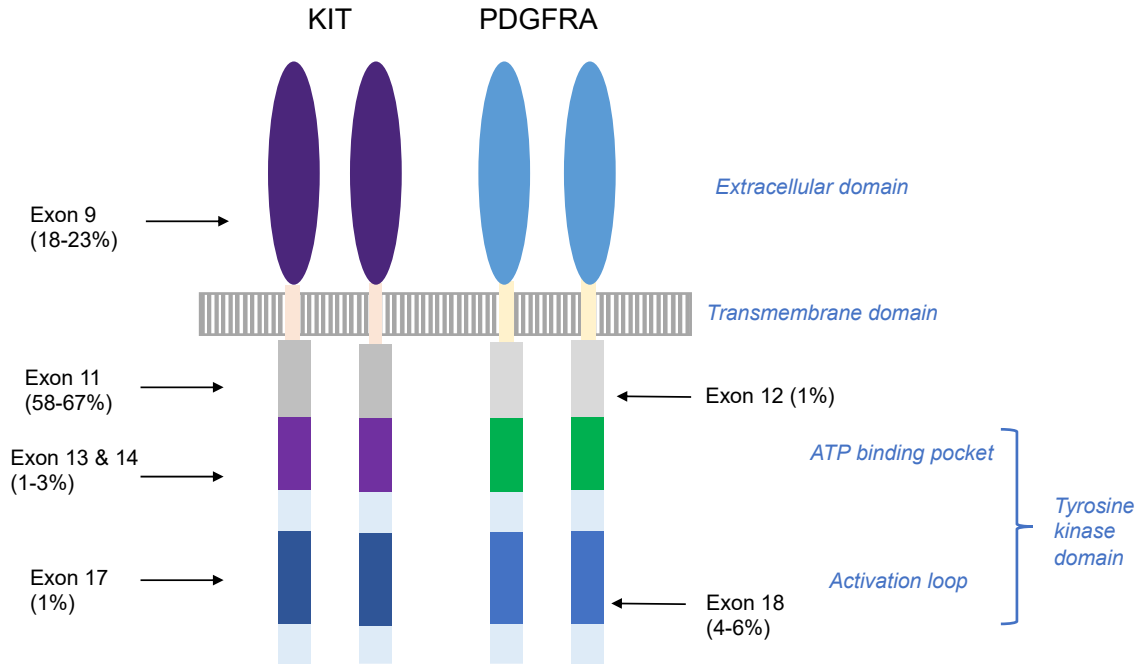
- Spindle cell (70%)
- Epithelioid (20%)
- Or pleomorphic (mixed) cells (10%)

Primary gain-of-function mutations in the receptor tyrosine kinase proto-oncogenes *KIT* (also referred to as CD117) and *PDGFRA* are key drivers that activate GIST development. Ninety-five percent of GISTs express the KIT receptor tyrosine kinase (CD117), and 70% are found to be positive for CD34 by immunohistochemistry (18). Approximately 80% of GISTs have primary mutations in *KIT*, and 5% to 10% have a mutation in homologous *PDGFRA* (14,19,20).

Of the *KIT* mutations, approximately 67% are located at exon 11 encoding the juxtamembrane receptor domain of the receptor, followed by exon 9 (18% to 23%) encoding the extracellular domain. Primary mutations rarely involve exon 13 or 14 for the cytoplasmic ATP-binding pocket (1% to 3%) or exon 17 for the activation loop (1%) (14,19,21).

For the smaller proportion of GISTs (5% to 10%) with a *PDGFRA* mutation, these mutations are commonly seen at exon 18 (~5%) and 12 (1%) and mostly occur in the stomach (Figure 2) (14). Tumours with exon 18 mutations at the D842V position are less aggressive and less likely to recur, yet are associated with resistance to the TKI, imatinib mesylate (19,22). *PDGFRA* D842V mutations occur in approximately 5% of patients (23).

Figure 2: Locations and frequency of primary KIT and PDGFRA mutations



Source: Adapted from Li and Raut 2019 (14) and Oppelt et al. 2017 (21).

DOG1 (ANO1) is strongly expressed in GISTs and is expressed in the majority (95%) of tumours. *KIT*-negative tumours are usually positive for DOG1 (19,23). Approximately 10% of GISTs lack mutations in *KIT* or *PDGFRA* genes and are referred to as wild-type (14,19). Wild-type GIST commonly express other genetic mutations in succinate dehydrogenase (*SDH*), *NF1*, and *BRAF* V600E (14,23). A small proportion of wild-type GISTs (approximately 4%) harbour an *ETV6-NTRK3* gene fusion mutation, which is seen in about 0.5% of all GIST cases overall (24).

Most primary *KIT* mutations involve a single mutation at diagnosis (19). Secondary acquired mutations can also occur over time in response to treatment with targeted TKI therapies, leading to treatment resistance (14,25). Primary and secondary mutations are a known issue in GIST, making it a heterogenetic disease in which a patient may have multiple mutations (14). Therefore, a treatment targeting both the primary and secondary *KIT* and *PDGFRA* mutations in GIST has strong potential for addressing multiple mutations.

B.1.3.2 Clinical presentation and burden of disease

GIST most frequently develops in the stomach or small intestine at proportions of approximately 60% to 70% and 25% to 35%, respectively (17,19,26,27). The colon and rectum are other rare sites involved in approximately 4% to 5% of cases (17,19). The median age at presentation of 62 years (26). GIST is not commonly seen in persons aged under 40 years (<10%) (17).

The clinical presentation of GISTs can vary based on the tumour size and site (26,28). The majority of patients present with symptoms at diagnosis, and approximately half have symptoms of acute or chronic GI bleeding (29–31). Symptoms are often non-specific and include GI pain, nausea, early satiety, abdominal bloating, anaemia, detection of abdominal mass, gastric discomfort or ulcer-like symptoms (15,26,28,29,32).

Common sites of GIST metastases are to the liver (65%) and peritoneum (21%). Less than 10% of tumours metastasise to the lung or bone (Table 3) (33). Metastasis to the lymph nodes rarely occurs and initial spread to extra-abdominal organs is uncommon (15,33). Extra-abdominal metastases typically occur later in advanced disease following long-term treatment with TKIs (28).

Table 3: Sites of GIST metastasis (n=94)

Site	Number of patients (%)
Liver	61 (65%)
Isolated to the liver only	50 (53%)
Peritoneum	20 (21%)
Lymph node	6 (6%)
Bone	6 (6%)
Lung	2 (2%)

Abbreviations: GIST – Gastrointestinal stromal tumour.
Source: DeMatteo et al. 2000 (33).

In a UK-based prospective database, 190 patients presented with histologically confirmed GIST. Patients were 52% male and the median age 64 years (range: 14-94), Only 4% of patients were <40 years old. The most common tumour site was the stomach (73%), followed by small bowel (16%), extra-gastrointestinal stromal tumour (4%), colorectal (3%), duodenum (3%) and oesophagus (1%). Histological subtypes were spindle cell (84%), mixed (12%) and epithelioid (4%). *KIT* exon 11 mutations were the most common mutation type (64%) (34).

The humanistic impact of GIST is substantial in affected patients. Disease progression to advanced stages often leads to a negative impact on HRQoL as well as reduction in cognitive and social functioning (35,36). Fifty-two percent of patients with GIST experience high levels of fear of disease progression, leading to cognitive and psychological distress and impairment (36). The psychological burden often leads to patients with GIST having difficulties in making and maintaining relationships, as well as experiencing body image concerns, low mood and depressive symptoms (35). Patients with advanced GIST are also functionally impaired, with 19% of patients found to have a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 (27,37).

The humanistic burden in patients with advanced GIST includes a high symptom burden as well as side effects associated with targeted TKI therapy. GIST is associated with multiple non-specific and disease-specific symptoms including pain, nausea, GI bleeding, abdominal bloating and fatigue (32). Thirty-nine percent of patients with GIST endure pain at least a few days a week, leading to a disruption in

activities of daily living in over half of patients (35). GIST patients who regularly suffer from pain are more likely to become upset or anxious (35).

Symptoms of GIST may be long-term and can also be accompanied by adverse events (AEs) of current GIST therapies, contributing to HRQoL deterioration (38). For example, 40% of patients being treated with a currently available TKI experience fatigue (39). As such, managing toxicities via dose reduction and maintaining HRQoL during TKI therapy is important (38).

Whilst the French EPIGIST observational study found HRQoL, as defined by the physical and mental component scores on the Short Form-36 (SF-36), was maintained or slightly improved with imatinib therapy in patients with unresectable or metastatic GIST, a progressive decline in HRQoL has been reported in the later-line treatment setting (38,40). In the international GRID phase 3 trial of advanced GIST patients receiving third-line (3L) or fourth-line (4L) treatment with regorafenib or placebo after progression on imatinib and sunitinib malate, EuroQol 5 dimensions (EQ-5D) utility scores declined with disease progression (Table 4) (38). Utility scores did not differ by treatment type (regorafenib or placebo) or cycle number, and regorafenib treatment did not lead to HRQoL improvements over placebo (38).

Table 4: EQ-5D utility values by disease progression, treatment type and cycle number

Parameter	Estimate	SE	Significance	95 % CI	
				Lower	Upper
Disease progression P0 (progression-free)	Reference category				
P1.0 (at progression)	-0.032	0.028	0.262	-0.087	0.024
P1.n (post-first progression)	-0.034	0.022	0.127	-0.077	0.010
P2 (post-second progression)	-0.182	0.061	0.003	-0.302	-0.061
Cycle number	-0.003	0.003	0.341	-0.009	0.003
Treatment type					
Regorafenib + BSC	Reference category				
Placebo + BSC	0.037	0.031	0.233	-0.024	0.097
Off-treatment	-0.013	0.039	0.749	-0.090	0.065

Abbreviations: BSC – Best supportive care; CI – Confidence interval; EQ-5D – EuroQol 5 dimensions; SE – Standard error.

Source: Poole et al. 2015 (38).

B.1.3.3 Clinical management of advanced GIST and place of ripretinib in the treatment pathway

Surgery for primary localised disease

Surgery is the recommended approach for primary and localised GIST and is the only potentially curative option (22,30,31). Immunohistochemistry assessments are conducted after tumour resection to assess risk of recurrence based on tumour site, size, and mitotic index (MI) (22). International guidelines, including UK clinical practice guidelines, recommend that small low-risk GISTs (<2 cm) can be either clinically watched and resected if they grow or become symptomatic, whilst all tumours ≥2 cm should be considered for surgical resection (5,15,30,41,42). A third of patients have an intermediate to high risk of disease progression and 50% have disease recurrence within 2 to 3 years following resection (29,43–45).

Patients at a high risk of disease recurrence following surgery of primary localised GIST can be treated with adjuvant imatinib at a dose of 400 mg once a day (QD) for 3 years, which has shown to reduce the risk of recurrence in this setting (22,30,43). NICE recommends imatinib as an option for adjuvant treatment for up to three years for adult patients who are at a high risk of relapse after surgery for KIT (CD117)-positive GISTs (46). High risk of relapse is defined by the criteria outlined by Miettinen 2006 (based on tumour size, location and mitotic rate) (12).

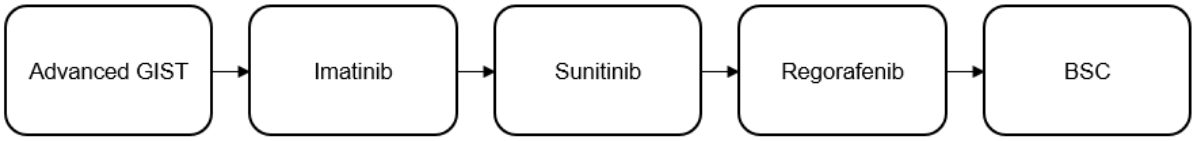
Metastatic or unresectable advanced GIST

Approximately half of patients present with metastatic or unresectable GIST at diagnosis and around 40% to 90% of surgical patients develop subsequent postoperative recurrence or metastasis (47,48). Targeted therapy with tyrosine kinase inhibitors (TKIs) is the standard of care for metastatic or unresectable GIST due to their anti-KIT and anti-PDGFRA properties. Conventional chemotherapy and radiotherapy are not effective in this advanced patient population (36,49,50).

In patients with metastatic or unresectable disease, imatinib is the standard treatment in England and Wales. 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 (2L) 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 (51). In addition, some imatinib-resistant patients have primary resistance to sunitinib due to the specific secondary mutation(s) that arise during imatinib treatment (52). Regorafenib is regarded as standard therapy for the third-line treatment of patients progressing on or failing to respond to imatinib and sunitinib. This treatment pathway is illustrated in Figure 3 (53–55).

Figure 3: Current clinical pathway for patients with advanced GIST



Abbreviations: BSC - Best supportive care; GIST – Gastrointestinal stromal tumour.

The British Sarcoma Group (BSG), the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) also provide guidelines for the treatment of advanced GIST (5,41,42). The BSG guidance for patients who have failed imatinib, sunitinib and regorafenib is that they be considered for participation in clinical trials of new agents. ESMO guidance states patients with metastatic GIST should be considered for participation in clinical trials of new therapies or combinations. There is limited instruction specific to GIST in the NCCN guidance for soft tissue sarcoma, but sorafenib, nilotinib, dasatinib, pazopanib, ripretinib and everolimus + TKI are presented as potential options. None of these options are approved for use in the UK for advanced GIST in the fourth-line. A UK clinician has confirmed that patients with GIST do not receive salvage therapy with previous therapies in the UK in the fourth-line or greater, unless treated privately.

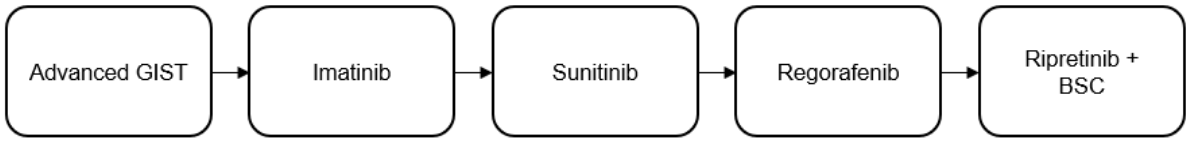
Place of ripretinib in the treatment pathway

There are currently no lines of pharmacological therapy recommended specifically for the treatment of patients with GIST who have received prior treatment with three or more kinase inhibitors, including imatinib, in the UK (56). There is no approved

treatment option for patients with advanced or unresectable GIST once patients have received imatinib, sunitinib, and regorafenib and experienced disease progression, or cannot tolerate regorafenib despite dose reductions. For patients who have progressed on the approved drugs, progression of KIT-driven tumours is primarily driven by development of further KIT resistant mutations. At present, there are no approved targeted therapies that broadly inhibit secondary drug-resistant mutations in GIST.

A high unmet medical need remains in the UK for a treatment which provides broad inhibition of KIT and PDGFRA kinase activity, including wild-type and multiple primary and secondary mutations associated with drug-resistant GIST in later lines of therapy, thereby blocking the drivers of resistance in advanced GIST (1,2). INVICTUS (NCT03353753) is the pivotal double-blind, randomised, placebo-controlled, phase 3 trial for ripretinib (see section B.2 Clinical effectiveness). Patients in the INVICTUS trial must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments (57,58). Ripretinib significantly improved median PFS compared with placebo and had an acceptable safety profile in patients with advanced GIST who were resistant to approved treatments. It is therefore proposed that the place of ripretinib would be in the fourth-line of treatment, alongside BSC, as shown in Figure 4.

Figure 4: Proposed future clinical pathway for patients with advanced GIST following the introduction of ripretinib



Abbreviations: BSC - Best supportive care; GIST – Gastrointestinal stromal tumour.

B.1.4 Equality considerations

There are no known equality issues relating to the use of ripretinib for treating advanced GIST after 3 therapies.

B.2 Clinical effectiveness

Summary of clinical effectiveness

Ripretinib has demonstrated an improvement in PFS (median PFS of 6.3 months vs 1.0 month for placebo), significantly reducing the risk of disease progression or death by 85% (HR 0.15; 95% CI 0.09 to 0.25]; p<0.0001) in the INVICTUS phase 3 randomised controlled trial (3)**.**

- Ripretinib has also showed a clinically meaningful improvement over placebo in OS (median OS 15.1 months vs 6.6 months; HR 0.36) (3).
- Median OS extended to 18.2 months in the ripretinib group versus 6.3 months in the placebo group (HR 0.41; 95% CI 0.26 to 0.65) from mature data of INVICTUS after an additional 19 months of follow-up from the primary analysis (data presented at ESMO September 2021) (4).

Ripretinib has demonstrated a clinically meaningful improvement in ORR by BICR. ORR was defined as complete response + partial response.

- In the ripretinib group, 8 (9.4%; 95% CI 4.2% to 17.7%; p=0.0504) of 85 patients had a confirmed objective response, all of whom had partial responses as assessed by BICR. None of the patients who received placebo had a confirmed objective response. Median duration of response had not been reached at the time of the study cut-off date (3).
- At 6 weeks, 66% of ripretinib-treated patients experienced stable disease vs 20% with placebo (3).
- The ORR was 11.8% (n=10 of 85 patients) in ripretinib-treated patients vs 0% in the placebo group after additional 9-months of follow-up (59). This improvement was maintained after an additional 19 months of follow-up (data presented at ESMO, September 2021) (4).

Ripretinib was generally well-tolerated and associated with an acceptable safety profile.

- The only serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anaemia (3.5%), nausea (2.4%), and vomiting (2.4%) (60).
- Rates of discontinuation, dose reduction and dose interruption due to adverse reactions were similar between ripretinib and placebo.
- Long-term safety findings after 19 months of additional follow-up were generally consistent with the primary analysis (data presented at ESMO, September 2021) (4).

Ripretinib-treated patients were able to maintain quality-of-life and function

- The results from the QoL instruments used showed clinically significant differences between ripretinib and placebo (3,61).
- Ripretinib-treated patients reported consistently stable EORTC QLQ-C30 physical and role functioning, as well as health ratings and QoL. In contrast, PROs declined sharply in the placebo arm (3,61).
- Outcome assessments that were pre-specified in the statistical analysis plan compared the change from Day 1 to Day 28 using EQ-5D-5L VAS and the EORTC QLQ-C30 questionnaire.
- Longitudinal change in outcomes scores from baseline in the ripretinib arm were measured. Patients receiving ripretinib reported stable scores on all pre-specified measures up to Cycle 10 indicating that ripretinib patients were able to maintain quality-of-life and function (61).
- When considering individual INVICTUS patients, the median time to definitive deterioration in the pre-specified PROs was greater than median PFS, suggesting that patients' use of ripretinib is not limited by toxicity (data presented at ISPOR, November/December 2021) (62).
- The median time until definitive deterioration estimates for physical/role functioning and the EQ-5D-5L VAS score were the same at 41.6 weeks for patients receiving ripretinib vs 7.9 weeks for patients receiving placebo (data presented at ISPOR, November/December 2021) (62).

B.2.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was originally conducted from January 2000 to 06 July 2020 to identify the clinical evidence relevant to ripretinib. The SLR was subsequently updated twice, first to cover the period of 2020 to 24 June 2021, then again to cover the period 24 June 2021 to 21 March 2022, to identify any recently published data. A health-related quality-of-life (HRQoL) SLR was also conducted for the same time periods, which identified HRQoL evidence relevant for inclusion in section B.2.

Please see Appendix D for details on the SLR methodology and process used to select the clinical evidence for ripretinib in the fourth and later-line setting (≥4L) for the treatment of gastrointestinal stromal tumour (GIST).

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified 25 publications, 11 of which were relevant to this submission. 9 of these publications were of one original phase 3, double-blind, placebo-controlled, randomised trial (INVICTUS), which provided direct head-to-head evidence on the clinical benefits of ripretinib + BSC versus placebo + BSC in patients with advanced unresectable or metastatic GIST who had progressed following imatinib, sunitinib, and regorafenib. This study is in line with the decision problem of this submission.

The publications reporting INVICTUS identified were from Blay et al. 2020 (Lancet Oncology) (3) and the corresponding erratum to this publication (63), a conference abstract by von Mehren et al. 2019 (Annals of Oncology) for the 44th European Society for Medical Oncology (ESMO) Congress 2019 (corresponding presentation identified through manual searches) (60), a conference abstract by Zalcberg et al. 2020 (Annals of Oncology) for the ESMO Virtual Congress 2020 (corresponding presentation also identified manually) (59), a presentation by Serrano et al. 2020 at the ESMO World Congress on Gastrointestinal Cancer (Virtual Meeting) (64), a publication by Zalcberg et al. 2021 (The Oncologist) (65), an abstract by Becker et al., 2022 (62), an abstract by Reichardt et al., 2021 (66), and an abstract by von Mehren et al., 2021 (4).

The SLR also identified two publications, Chi et al. 2019 (67) and Janku et al., 2020 (68), relating to the phase 1, non-randomised study (NCT02571036) of ripretinib that

included a dose escalation and expansion phase of patients with GIST in the 2L, 3L, and ≥4L setting who were treated with ripretinib at the 150 mg QD dose (67). Efficacy and safety results were broadly consistent with the INVICTUS trial and are not discussed further in this submission.

The HRQoL SLR identified two further publications reporting HRQoL analyses of INVICTUS, in addition to Blay et al. 2020, Becker et al., 2021, and Reichardt et al., 2021. These were both posters presented at the 2020 ASCO Annual Virtual Meeting by Heinrich et al. 2020 (61) and George et al. 2020 (66).

The publications of INVICTUS listed above reported results for the primary cut-off date of 31 May 2019, except for 3 publications. The abstract by Zalcberg et al. 2020, which reported updated results as of 9 March 2020, covering an additional 9 months since the primary results analysis, and the publication by Zalcberg et al. 2021, which reported updated results as of 10 August 2020 for patients in the ripretinib group who dose escalated. The abstract by von Mehren et al., 2021 reported a long-term update of mature data, with a data cut-off date 19 months after the primary analysis.

The INVICTUS clinical study report (CSR) and statistical analysis plan (SAP) are two other documents that have been used to inform reporting of the phase 3 study, however, they were not identified in literature searches due to not being publicly available.

The full list of publications used in this submission to present the efficacy and safety results of ripretinib in INVICTUS are listed in Table 5.

Table 5: Trials and key reports presented in the submission (INVICTUS)

Report/citation
Clinical SLR
Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology.* 2020;21(7):923–34 (3)
Correction to *Lancet Oncol* 2020;21:923–34. The Lancet Oncology. 21(7) (pp e341), 2020. Date of Publication: July 2020 (63)
Serrano C, Heinrich MC, George S, et al. Efficacy and safety of ripretinib as ≥4th-line therapy for patients with gastrointestinal stromal tumor (GIST) following crossover from placebo: Analyses from INVICTUS [Presentation]. Presentation at the ESMO World Congress on Gastrointestinal Cancer Virtual Meeting; 2020 July 1-4 (64)

Report/citation
von Mehren M, Serrano C, Bauer S, et al. INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as ≥ 4th-line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). *Annals of Oncology*. 2019;30(Supplement 5):v925-v926. Presentation at the 44th ESMO Congress. Spain (60)
Zalcberg JR, Heinrich M, George S, et al. Clinical benefit with ripretinib as ≥ 4th line treatment in patients with advanced gastrointestinal stromal tumors (GIST): Update from the phase III INVICTUS study. *Annals of Oncology.* 2020;31(Supplement 4):S973-S974. Presentation at ESMO Virtual Congress 2020 (59)

Report/citation
Zalcberg JR, Heinrich MC, George S, et al. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. *The Oncologist.* 2021;9999:1-11 (65)
von Mehren M, Heinrich MC, George S, Zalcberg JR, Bauer S, Gelderblom H, Schöffski P, Serrano C, Jones RL, Attia S, D'Amato G. 1540P Ripretinib as≥ 4th-line treatment in patients with advanced gastrointestinal stromal tumor: Long-term update from the phase III INVICTUS study. Annals of Oncology. 2021 Sep 1;32:S1120-1.
Becker C, Harrow B, Heinrich MC, Schöffski P, Serrano C, Vincenzi B, Blay JY. POSB342 Time Until Definitive Deterioration (TUDD) in Patient Reported Outcomes (PROS) in a Phase 3 Trial for Ripretinib in 4L Patients with Gastrointestinal Stromal Tumour (GIST). Value in Health. 2022 Jan 1;25(1):S227.
Reichardt P., Heinrich M., George S., Zalcberg J.R., Bauer S., Gelderblom H., Schöffski P., Serrano C., Jones R.L., Attia S., D'Amato G., Chi P., Lacouture M.E., Cha E., Meade J.N., Ruiz-Soto R., Blay J.-Y., Von Mehren M. Safety profile of ripretinib, including impact of alopecia, and palmar-plantar erythrodysesthesia syndrome (ppes) on patient-reported outcomes (PROS), in >= fourth-line advanced gastrointestinal stromal tumors (Gist): Analyses from invictus. Oncology Research and Treatment. Conference: Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie. Berlin Germany. 44(SUPPL 2) (pp 186-187), 2021. Date of Publication: 2021.
QoL SLR
Heinrich MC, George S, Zalcberg J, et al. Quality of life (QoL) and self-reported function with ripretinib in ≥4th line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS [Poster 423]. Poster presented at the 2020 ASCO Annual Virtual Meeting; 2020 May 29-31 (61)
George S, Heinrich MC, Zalcberg J, et al. Safety profile of ripretinib, including impact of alopecia and palmar-plantar erythrodysaesthesia syndrome (PPES) on patient reported outcomes (PROs), in ≥4th line advanced gastrointestinal stromal tumors (GIST): Analyses from INVICTUS [Poster 427]. Poster presented at the 2020 ASCO Annual Virtual Meeting; 2020 May 29-31 (66)
Internal reports
Deciphera Pharmaceuticals. 2019. DOF: Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have received treatment with prior anticancer therapies (INVICTUS) [Clinical Study Report] (69)
Deciphera Pharmaceuticals. 2019. DOF: Statistical Analysis Plan; Protocol No. DCC-2618-03-001. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with Advanced Gastrointestinal Stromal Tumors who have Received Treatment with Prior Anticancer Therapies [Final Version 2.0] (70)

Details of the phase 3 INVICTUS randomised controlled trial (RCT) identified in SLR searches are provided in Table 6.

Table 6: Clinical effectiveness evidence

Study	INVICTUS (NCT03353753)				
Study design	Phase 3, multicentre, double-blind, placebo-controlled, randomised trial				
Population	Patients with GIST aged ≥18 years, ECOG PS of 0-2, and with disease progression on imatinib, sunitinib, and regorafenib (fourth-line or later).				
Intervention(s)	Ripretinib + BSC				
Comparator(s)	Placebo + BSC				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale for use/non-use in the model	INVICTUS is the key trial providing efficacy and safety data concerning the use of ripretinib in patients with advanced GIST who have received prior treatment with three or more kinase inhibitor inhibitors, including imatinib				
Reported outcomes specified in the decision problem	PFS, OS, AEs and HRQoL				
All other reported outcomes	N/A				

Abbreviations: AE − Adverse event; BSC − Best supportive care; ECOG PS − Eastern Cooperative Oncology Group Performance Status; GIST − Gastrointestinal stromal tumour; HRQoL – Health-related quality-of-life; OS − Overall survival; PFS − Progression-free survival

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

INVICTUS is an international, multicentre, randomised, double-blind, placebo-controlled phase 3 trial in 129 patients who had received ≥3 prior anticancer therapies for advanced GIST comparing the efficacy of ripretinib plus best supportive care (BSC) (hereafter referred to as 'ripretinib' group) and placebo plus BSC (hereafter referred to as the 'placebo' group) in patients who had received prior treatment with at least imatinib, sunitinib, and regorafenib (3). The study was conducted at 29 specialised hospitals across 12 countries across North America, Europe, and Asia (3).

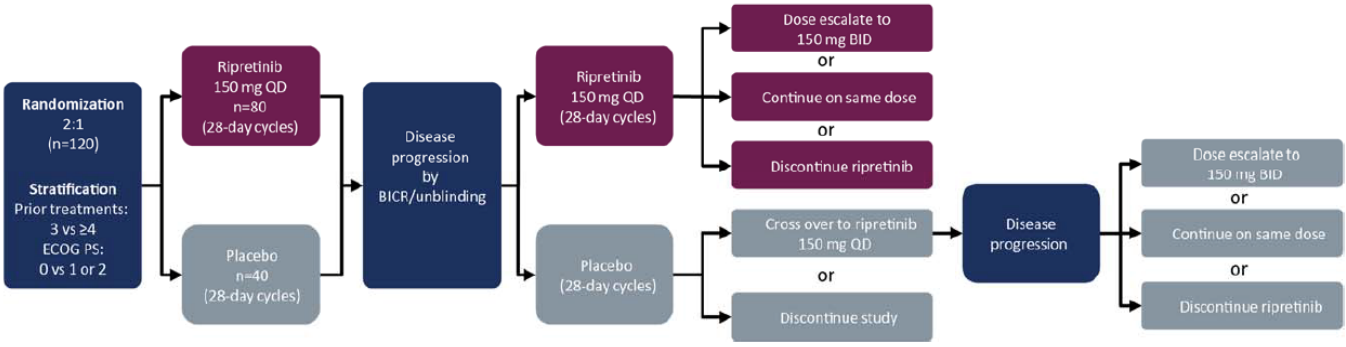
Patients were randomised 2:1 to receive ripretinib 150 mg once a day (QD) or placebo in 28-day cycles until disease progression or unacceptable toxicity. Randomisation was stratified by (3):

- Patients who had received 3 versus ≥4 prior anticancer treatments
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 versus 1 or 2

[redacted]

Patients, investigators, and research staff were unblinded to the study drug assignment upon disease progression, as determined by BICR. Patients randomised to ripretinib 150 mg QD were given the option to continue at an increased dose (150 mg twice a day [BID]), to continue their current dose at 150 mg QD, or to discontinue treatment with ripretinib (3). Patients randomised to placebo were able to cross over to ripretinib 150 mg QD or discontinue the study (Figure 5) (3). Patients had a follow-up safety visit 30 days after their final dose, and were followed up every 3 months thereafter to collect long-term survival data (3).

Figure 5: INVICTUS study design and treatment allocation



Abbreviations: BID − Twice a day; BICR – Blinded independent central review; ECOG PS − Eastern Cooperative Oncology Group 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 (3), supplementary appendix, figure S1.

For the primary analysis, the efficacy and safety of ripretinib compared with placebo/BSC is based on the double-blind period for the primary completion cut-off date of 31 May 2019. This is except for OS, which is analysed for the entire on-study period and followed patients until they died. OS analyses include data from both the double-blind and open-label periods (3).

Primary and secondary endpoints

The primary efficacy endpoint in the study was PFS, defined as the date from randomisation to the date of progressive disease or death due to any cause, as

assessed by radiologic BICR using the mRECIST version 1.1 criteria (3). The key secondary efficacy endpoint was objective response rate (ORR), defined as a confirmed complete response (CR) and partial response (PR), as assessed by BICR and during the initial assigned study treatment (3). These were pre-specified analyses in the SAP.

Other secondary endpoints were OS, time to progression (TTP), time to best response, duration of response (DOR), HRQoL as assessed using the EuroQol 5 dimensions 5 levels [EQ-5D-5L], EuroQol visual analogue scale (EQ-VAS), and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30) - physical and role functioning domains only), and safety (3).

Safety assessments included clinical laboratory tests, ECOG performance status, vital signs, weight, 12-lead electrocardiogram (ECG) measurements, left ventricular ejection fraction, physical examinations, and dose reductions, interruptions, or treatment discontinuations (3).

The cost-effectiveness model uses PFS, OS, EQ-5D-5L and AE outcomes – see section B.3 Cost effectiveness.

Eligibility

Patients enrolled in INVICTUS were aged 18 years and older who had a histologically confirmed diagnosis of GIST, at least 1 measurable lesion based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 criteria, an ECOG performance status of 0 to 2, and had progressed on at least imatinib, sunitinib, and regorafenib, or were intolerant to these therapies despite dose modifications. Patients were excluded if they had received an anticancer therapy within 14 days of the study. Key inclusion and exclusion criteria are presented in Table 7 (3).

Table 7: Inclusion and exclusion criteria of INVICTUS

Inclusion criteria	Exclusion criteria
Aged ≥18 years Histologic diagnosis of GIST Patients must have progressed on imatinib, sunitinib, and regorafenib or have	Treatment with anticancer therapy, including investigational therapy or investigational procedures, within 14 days or 5x the half-life (whichever was longer) prior to the first dose of study drug

documented intolerance to any of these treatments ECOG PS of 0 to 2 at screening At least 1 measurable lesion according to the mRECIST v1.1 criteria* within 21 days of the first dose of study drug Adequate organ function and bone marrow reserve	

Abbreviations: GIST − Gastrointestinal stromal tumour; ECOG PS − Eastern Cooperative Oncology Group Performance Status; mRECIST v1.1 − modified Response Evaluation Criteria in Solid Tumors version 1.1.
Source: Blay et al. 2020 (3).

Patient baseline characteristics

Patient characteristics were generally well-balanced across the two treatment groups (3). There was a similar proportion of males (55% vs 59%), patients in the ECOG performance status strata of 1 or 2 (56% vs 61%) and patients with three prior lines of therapy (64% vs 61%) between the ripretinib and placebo groups, respectively. In both groups, over half of patients were outside the US (53% vs 55%) and the median age was 59 and 65 years, respectively (Table 8) (3).

The ripretinib group had a lower proportion of patients aged ≥75 years than the placebo group (9% vs 23%) and a slightly higher frequency of primary gastric tumours (47% vs 41%). A slightly lower frequency of KIT exon 11 mutations was seen in the ripretinib group (55% vs 64%) and PDGFRA mutations were present in 4% in the ripretinib group and none in the placebo group (3).

Table 8: Patient baseline characteristics in INVICTUS - double-blind period (ITT population)

	Ripretinib group (n=85)	**Placebo group (n=44)**
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%)

	Ripretinib group (n=85)	Placebo group (n=44)
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%)

Abbreviations: ECOG PS − Eastern Cooperative Oncology Group Performance Status; ITT − Intent-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 (3), table 1.

The methodology of INVICTUS is summarised in Table 9.

Table 9: Summary of the INVICTUS methodology

INVICTUS (NCT03353753)	**Trial 1**
Location	Multinational
Trial design	Phase 3, double-blind, randomised, placebo-controlled, trial
Eligibility criteria for	Aged ≥18 years

INVICTUS (NCT03353753)	Trial 1
participants	Histologic diagnosis of GIST Patients must have progressed on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments ECOG PS of 0 to 2 at screening
Settings and locations where the data were collected	29 specialised hospitals in North America, Europe, and Asia
Trial drugs	Ripretinib 150mg QD + BSC (n=85) Matching placebo 150 mg QD + BSC (n=44)
Primary outcome (including scoring methods and timings of assessments)	PFS, as assessed by BICR. Tumour assessments were conducted at screening and then every cycle through Cycle 4. After Cycle 4 (or if patient on ripretinib after unblinding), assessments were done every other cycle.
Other outcomes used in the economic model/specified in the scope	PFS, OS, AEs and HRQoL
Pre-planned subgroups	Subgroup analyses of the primary endpoint of PFS were pre-specified. The following subgroup analyses were performed: Age (18 to 64 vs 65 to 74 vs 75 years or older) Gender (Male vs Female) Race (White vs non-White vs not reported) Region (US vs non-US) Screening ECOG PS (0 vs 1 or 2) Number of prior therapies (3 vs ≥4)

Abbreviations: AE − Adverse event; BICR − Blinded independent central review; BSC − Best supportive care; ECOG PS − Eastern Cooperative Oncology Group Performance Status; GIST − Gastrointestinal stromal tumour; HRQoL – Health-related quality-of-life; OS − Overall survival; PFS − Progression-free survival; QD − Once a day.
Source: Blay et al. 2020 (3).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The primary efficacy endpoint in the study was PFS, defined as the date from randomisation to the date of progressive disease or death due to any cause, as assessed by radiologic BICR using the mRECIST version 1.1 criteria.

Primary efficacy analyses were based on the intent-to-treat (ITT) population, defined as all randomised patients (N=129) (3). The safety population was used for safety analyses and included all patients who received at least one dose of study drug (N=128) (3).

A sample size of 120 patients (ripretinib, n=80; placebo, n=40) was calculated to provide both power for efficacy and size for the safety database with an assumed 15%

patient dropout (3). [redacted] The p-value was from a 2-sided stratified log-rank test at 0.05 significance level in testing the hypothesis of no difference between ripretinib and placebo to provide over 90% power to detect a difference in PFS between ripretinib and placebo (3). This power assumed a median PFS of 4.5 months for ripretinib and 1.0 month for placebo and approximately 80% power to detect a 20% difference in objective response, assuming an ORR of 22% and 2% for ripretinib and placebo, respectively (3).

A Cox regression model was used to obtain the point estimate of the hazard ratio (HR) with treatment and randomisation stratification factors as fixed factors and its 95% CI was obtained using Wald method. PFS time was summarised using the Kaplan-Meier methodology, with associated 2-sided 95% CIs. The proportional hazards assumption was examined by visual inspection of the log (-log) plot (3). The same methodology was used for other time-to-event endpoints (PFS, OS, TTP, and time to best response).

To control for family-wise type I error, a statistical hierarchical testing procedure was used. The hypothesis tests to evaluate the difference between the two treatment groups were done at a 2-sided 0.05 level of significance sequentially in the following order (3):

1. The primary endpoint - PFS
2. The key secondary endpoint - ORR
3. OS
4. HRQoL for change from baseline to Cycle 2 on Day 1 in the physical and role functioning domains of the EORTC QLQ-C30 (each at 0.025 level of significance)

If a hypothesis test was found to be non-significant at the α=0.05 level, subsequent analyses in the hierarchy were reported as descriptive statistics (3). Other endpoints (e.g. TTP, time to best response) were not included in the hierarchy due to insufficient power (3).

ORR was analysed by an unstratified two-sided Fisher's exact test (using a 0.05 significance level) to evaluate treatment difference, and the 95% CI of the treatment difference was calculated with the Newcombe method. Descriptive statistics were used to summarise safety data and HRQoL variables (3). HRQoL outcome

assessments that were pre-specified in the SAP compared the change from baseline to Cycle 2 Day 1 in scores on the EQ-5D-5L, EQ-VAS and the EORTC QLQ-C30 questionnaires (70). A t-test was conducted to evaluate changes between groups in EQ-VAS scores from baseline to Cycle 2 Day 1. Analysis of covariance models (ANCOVA) were used to assess change from baseline to Cycle 2 Day 1 in role and physical function domain scores between groups on the EORTC QLQ-C30 (3). EQ-5D-5L was summarised overall by number and percentage for each level of each dimension. For the EQ-5D-5L index (utility) score, an ANCOVA model was used assess change from baseline to Cycle 2 Day 1 between groups (70).

Handling of missing data

Patients who had first disease progression or died after two or more consecutive missed/non-evaluable assessments were censored for the primary PFS endpoint at the time of radiologic assessment immediately prior to the two or more consecutive missed/non-evaluable radiologic assessments. For the secondary endpoint of ORR, patients with an unknown or missing response were categorised as non-responders and were included in the denominator when calculating the proportion (70)

Subgroup analyses

Subgroup analyses of the primary endpoint of PFS were pre-specified (3). In each subgroup, the HR was from Cox regression with treatment as a fixed factor, and the 95% CI of the HR was based on the Wald method. The following subgroup analyses were performed (3):

- Age (18 to 64 vs 65 to 74 vs 75 years or older)
- Gender (Male vs Female)
- Race (White vs non-White vs not reported)
- Region (US vs non-US)
- Screening ECOG performance status (0 vs 1 or 2)
- Number of prior therapies (3 vs ≥4)

The subgroup analysis of OS on crossover was post hoc. The survival curves and median OS of the subgroups are based on the Kaplan-Meier method.

Please refer to Appendix D for details on the CONSORT diagram of patients eligible for enrolment into INVICTUS.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

INVICTUS was a double-blind, parallel-group, randomised, placebo-controlled study, which is the gold-standard study design for interventional clinical trials that minimises the risk of confounding factors and allows direct comparison of the relative efficacy of interventions. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice (3). Randomisation was carried out appropriately, with patients, assessors, and investigators and site staff all blinded to treatment assignment during the double-blind period. There were no imbalances in drop-outs between groups and primary efficacy analyses were based on the ITT population. Therefore, the trial design of INVICTUS was sufficiently robust to answer the decision problem, in assessing ripretinib versus BSC in patients with advanced GIST in the fourth- or later-line setting (≥4L).

Please refer to Appendix D for complete details on the quality assessment.

B.2.6 Clinical effectiveness results of INVICTUS

Results presented for primary analyses are for the double-blind period until the data cut-off of 31 May 2019 (3). OS analyses included data from both the double-blind and open-label periods (i.e., total time on treatment). All efficacy analyses were conducted on the ITT population, defined as all randomised patients who provided informed consent (3).

Results for PFS, OS and safety during the open-label period are also available and have been reported separately. Additional longer-term analyses involving an additional 9-months of follow-up are available, with a data cut-off of 9 March 2020 (59).

The median relative dose intensity in the double-blind period was 100% (IQR 98.1 to 100.0) for the ripretinib group and 97% (86.5 to 100.0) for the placebo group. Based on the ITT population, 66% of patients randomised to placebo switched to ripretinib after disease progression (n=29 of 44 patients; 15 patients did not switch to ripretinib) (3). [redacted]

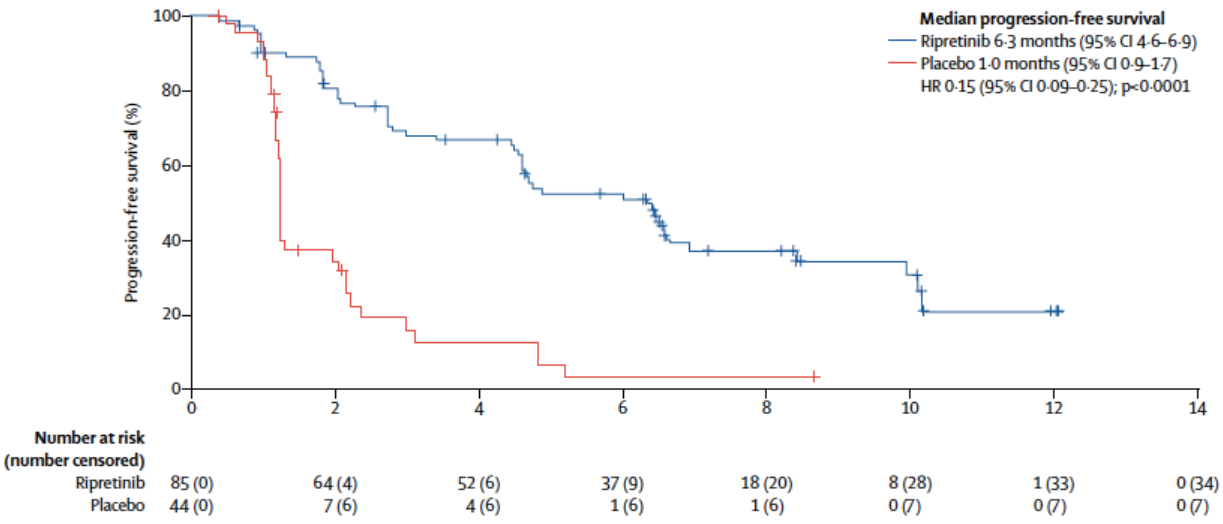
PFS – primary endpoint

At the 31 May 2019 data cut-off, the median follow-up time in the double-blind period was 6.3 months (interquartile range [IQR] 3.2 to 8.2) for the ripretinib group and 1.6 months (1.1 to 2.7) for the placebo group (3).

The primary endpoint of PFS was achieved with a median PFS of 6.3 months (95% CI 4.6 to 6.9 months) in the ripretinib 150 mg QD group versus 1.0 month (95% CI 0.9 to 1.7 months) for the placebo arm, as assessed by BICR (3). This represents a more than 6-fold increase in PFS with ripretinib compared with placebo in an advanced, heavily pre-treated patient population. Patients treated with ripretinib had a significantly reduced risk of disease progression or death by 85% compared with placebo (HR 0.15; 95% CI 0.09 to 0.25; p<0.0001) (3).

The Kaplan-Meier curve for PFS is shown in Figure 6.

Figure 6: Kaplan-Meier PFS curve as assessed by BICR (ITT population)



Abbreviations: BICR − Binded independent central review; CI − Confidence interval; HR − Hazard ratio; ITT − Intent-to-treat; PFS − Progression-free survival

Note: crosses denote censoring of data.

Source: Blay et al. 2020 (3), page 928, figure 2A

After 6 months, 51% (95% CI 39.4% to 61.4%) of patients in the ripretinib group were estimated to have PFS and 3.2% for the placebo group (95% CI 0.2% to 13.8%) (3). Disease progression or death (PFS event) occurred in 60% of patients in the ripretinib group (34 [40%] of patients were censored) and in 84% in the placebo group (seven

[16%] patients were censored) (3). PFS results for the double-blind analysis period are summarised in Table 10.

Table 10: Summary of PFS results as assessed by BICR (ITT population)

	Ripretinib (n=85)	Placebo (n=44)
PFS event n (%)	51 (60%)	37 (84%)
Patients censored n (%)	34 (40%)	7 (16%)
Median PFS (95% CI)	6.3 months (4.6 to 6.9)	1.0 month (0.9 to 1.7)
HR (95% CI)*	0.15 (0.09 to 0.25)	
p-value**	p<0.0001	

Abbreviations: BICR − Blinded independent central review; CI − Confidence interval; HR − Hazard ratio; ITT − Intent-to-treat; PFS − Progression-free survival.

* Calculated using Cox regression model, which includes treatment and randomisation stratification factors as fixed factors; 95% CI is based on Wald method.

** p-value is based on 2-sided stratified log-rank test.

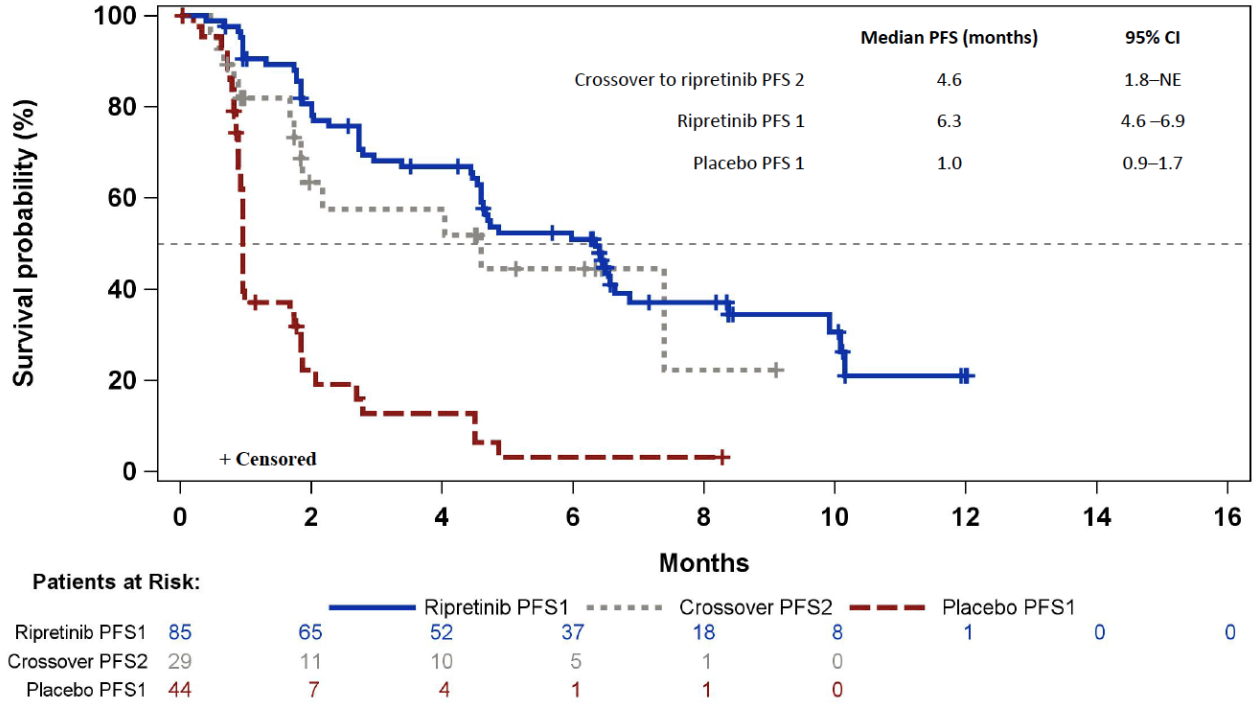
Source: Blay et al. 2020 (3), page 929, column 1, paragraph 2 and page 928, figure 2A.

Median PFS results from the more recent data cut-off periods of 09 March 2020 and 15 January 2021 were similar to those reported for the primary analysis period, with a median PFS of 6.3 months (95% CI 4.6 to 8.1 months) in the ripretinib group versus 1.0 month (95% CI 0.9 to 1.7 months) in the placebo group (HR 0.16; 95% CI 0.10 to 0.27) at both time points (4,59).

Open-label PFS (exploratory analysis)

An exploratory analysis of PFS in the open-label period was conducted for the 29 patients originally randomised to placebo in the double-blind period who crossed over to ripretinib 150 mg QD (64). Median PFS was 4.6 months (95% CI 1.8 months to not estimable [NE]). Of the 29 patients, 45% (n=13) had a PFS event and 55% (n=16) were censored. Patients who crossed over experienced a benefit as early as 1 month after initiating treatment with ripretinib (Figure 7 and Table 11) (64).

Figure 7: Exploratory PFS in patients (n=29) crossing over to ripretinib 150 mg QD in the open-label period



Abbreviations: CI – Confidence interval; PFS – Progression-free survival; QD – Once a day.

PFS1 indicates PFS during the double-blind period and PFS2 indicates cross over patient's time from ripretinib initiation to progression or death.

Source: Serrano et al. 2020 World Congress on Gastrointestinal Cancer, virtual conference (64), slide 9.

Table 11: Exploratory analysis of PFS following cross over from placebo to ripretinib 150 mg QD compared with PFS outcomes in the double-blind period

	Open-label period	Double-blind period	
	Cross over to ripretinib PFS2 (n=29)	Ripretinib PFS1 (n=85)	Placebo PFS1 (n=44)
PFS event n (%)	13 (45%)	51 (60%)	37 (84%)
Patients censored n (%)	16 (55%)	34 (40%)	7 (16%)
Median PFS (95% CI)	4.6 (1.8 to NE)	6.3 (4.6 to 6.9)	1.0 (0.9 to 1.7)

Abbreviations: CI – Confidence interval; PFS – Progression-free survival; NE – Not estimable; QD – Once a day.

PFS1 indicates PFS during the double-blind period and PFS2 indicates cross over patient's time from ripretinib initiation to progression or death.

Source: Serrano et al. 2020 World Congress on Gastrointestinal Cancer, virtual conference (64), slide 9.

ORR – key secondary endpoint

In the ripretinib group, 9.4% (n=8; 95% CI 4.2% to 17.7%) of patients had a confirmed objective response as assessed by BICR in the double-blind analysis period, compared with no patients in the placebo group. Results for ORR did not reach statistical significance in the study with the majority of the patients having PR and stable disease. No CRs were recorded (3). Of those who achieved an objective

response with ripretinib, all patients had a PR (3). A higher proportion of ripretinib patients had stable disease at 6 weeks compared with placebo (66% vs 20%) and fewer had disease progression (16 vs 28 patients) (3). Response rates are summarised in Table 12.

In updated analyses after an additional 9 and 19 months of follow-up (data cut-off 09 March 2020 and 15 January 2021, respectively), ORR rates were 11.8% (95% CI 5.8% to 20.6%) versus 0% (95% CI 0% to 8.0%) in the ripretinib and placebo groups, respectively (4,59).

Table 12: ORR as assessed by BICR (ITT population)

Response	Ripretinib (n=85)		Placebo (n=44)		P-value*
	n (%)	95% CI	n (%)	95% CI	
Confirmed OR	8 (9%)	4% to 18%*	0 (0%)	0% to 8%*	0.0504
CR	0 (0%)	0% to 4%	0 (0%)	0% to 8%	-
PR	8 (9%)	4% to 18%	0 (0%)	0% to 8%	-
SD (6 weeks)	56 (66%)	55% to 76%	9 (20%)	10% to 35%	-
SD (12 weeks)	40 (47%)	36% to 58%	2 (5%)	1% to 16%	-
PD	16 (19%)	11% to 29%	28 (64%)	48% to 78%	-
Not evaluable	4 (5%)	-	3 (7%)	-	-
No response assessment	1 (1%)	-	4 (9%)	-	-

Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; CR – Complete response; ITT – intent-to-treat; OR – Objective response; ORR – Objective response rate; PD – Progressive disease; PR – Partial response; SD – Stable disease.

* p-value is based on Fisher's exact test.

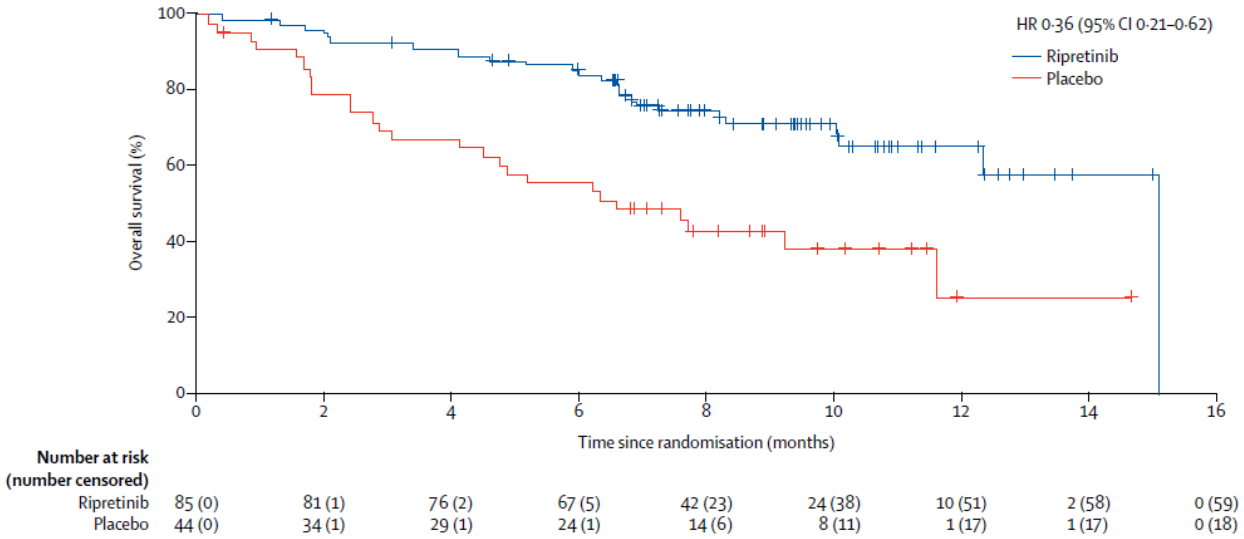
Source: Blay et al. 2020 (3), page 929, table 2.

OS – secondary endpoint

OS analyses were conducted for the entire on-treatment period, including both the double-blind and open-label periods. Patients achieved a clinically meaningful survival benefit when treated with ripretinib versus patients on placebo. The median OS was 15.1 months (95% CI 12.3 to 15.1 months) in the ripretinib group and 6.6 months (95% CI 4.1 to 11.6 months) in the placebo group, inclusive of the double-blind and open-label periods. Ripretinib reduced the risk of death by 64% versus placebo (HR 0.36; 95% CI 0.21 to 0.62; Figure 8) (3). At 12 months, estimated OS was 65.4% (95% CI 51.6% to 76.1%) for the ripretinib group and 25.9% (95% CI 7.2% to 49.9%) for the placebo group (3).

The OS endpoint was not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints of ORR and OS. Ripretinib led to an OS benefit in both the double-blind and open-label periods (refer to post hoc analysis in section B.2.7 Subgroup analysis).

Figure 8: OS in the double-blind and open-label periods*



Abbreviations: CI – Confidence interval; HR – Hazard ratio; OS – Overall survival.

* Owing to the hierarchical testing procedures of the endpoints, OS endpoint could not be formally tested because the objective response rate was not statistically significant.

Source: Blay et al. 2020 (3), page 928, figure 2B.

By the primary data cut-off period, 31% of patients in the ripretinib group (59 censored), and 59% of patients in the placebo group (18 censored) had died (OS event; Table 13) (3).

Table 13: Summary of OS results (ITT population)

	Ripretinib (n=85)	**Placebo (n=44)**
OS event n (%)	26 (31%)	26 (59%)
Patients censored	59 (69%)	18 (41%)
Median OS (95% CI)	15.1 months (12.3 to 15.1)	6.6 months (4.1 to 11.6)
HR (95% CI)*	0.36 (0.21 to 0.62)	

Abbreviations: CI – Confidence interval; HR – Hazard ratio; ITT – Intent-to-treat; OS – Overall survival.

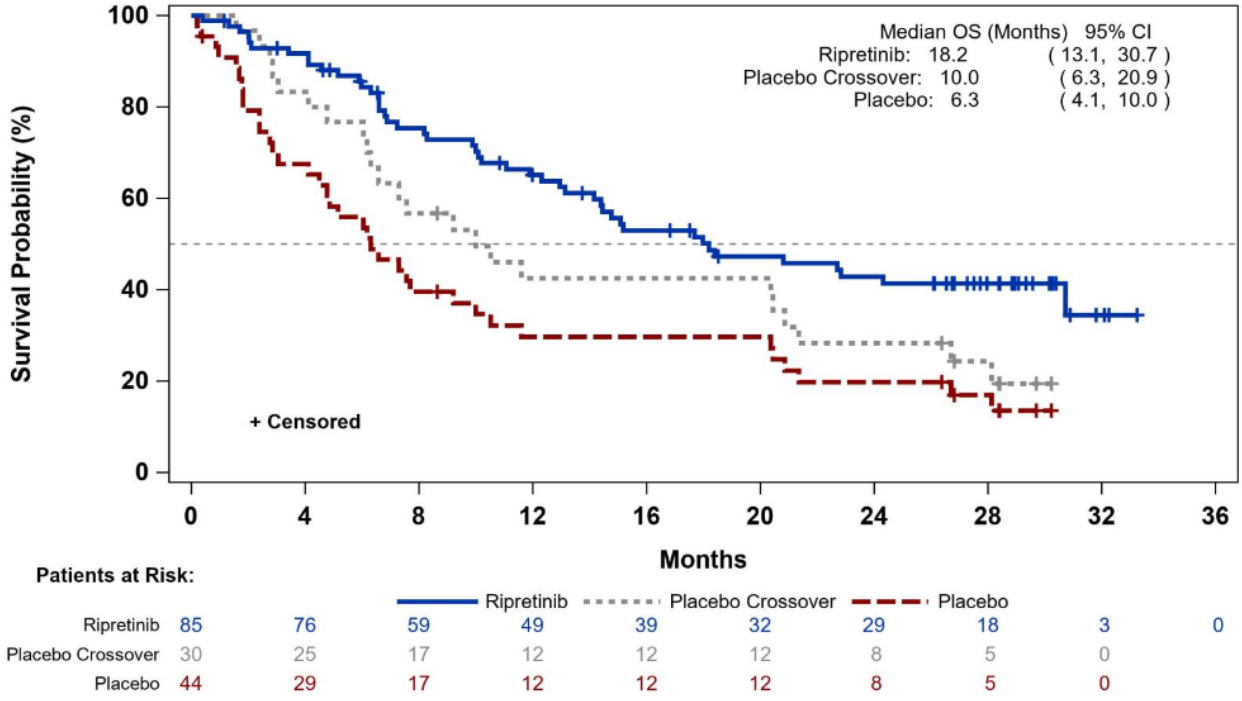
* Calculated using the Cox regression model, which includes treatment and randomisation stratification factors as fixed factors; 95% CI based on Wald method.

Note: OS is defined as the time interval between the date of randomisation until the date of death or censored at the date of last follow-up; patient groups are based on the treatment initially assigned. Due to the hierarchal testing procedure of the endpoints, OS could not be formally tested for statistical significance because the objective response was not significant; the nominal p-value displayed is based on 2-sided stratified log-rank test.

Source: Blay et al. 2020 (3), page 929, column 1, paragraph 4.

Median OS in the ripretinib group extended from 15.1 months to not reached after an additional 9 months follow-up (95% CI 13.1 months to NE). Median OS in the placebo group remained similar to that reported in the primary analysis period at 6.3 months (95% CI 4.1 to 10.0 months; HR 0.42; 95% CI 0.26 to 0.67) (59). From mature OS data for the most recent data cut-off (15 January 2021), median OS was reached and further extended to 18.2 months in the ripretinib group (95% CI 13.1 to 30.7 months; Figure 9). Median OS remained the same in the placebo group (6.3 months; 95% CI 4.1 to 10.0 months; HR 0.41; 95% CI 0.26 to 0.65) and in patients crossing over from placebo to ripretinib in the open-label period, median OS was 10 months (95% CI 6.3 to 20.9; Figure 9) (4).

Figure 9: Mature OS from extended follow-up (data cut-off 15 January 2021)



Abbreviations: CI – Confidence interval; OS – Overall survival.

Source: von Mehren et al. 2021, slide 13 (presented at ESMO, September 16-21, 2021) (4).

Median OS increased in the ripretinib group at these later follow-up dates, reflecting more mature data, indicating improved survival with long-term ripretinib treatment. These data support the clinically meaningful survival benefit with ripretinib.

The low median OS observed with placebo reflects the aggressive nature of GIST in patients with advanced GIST.

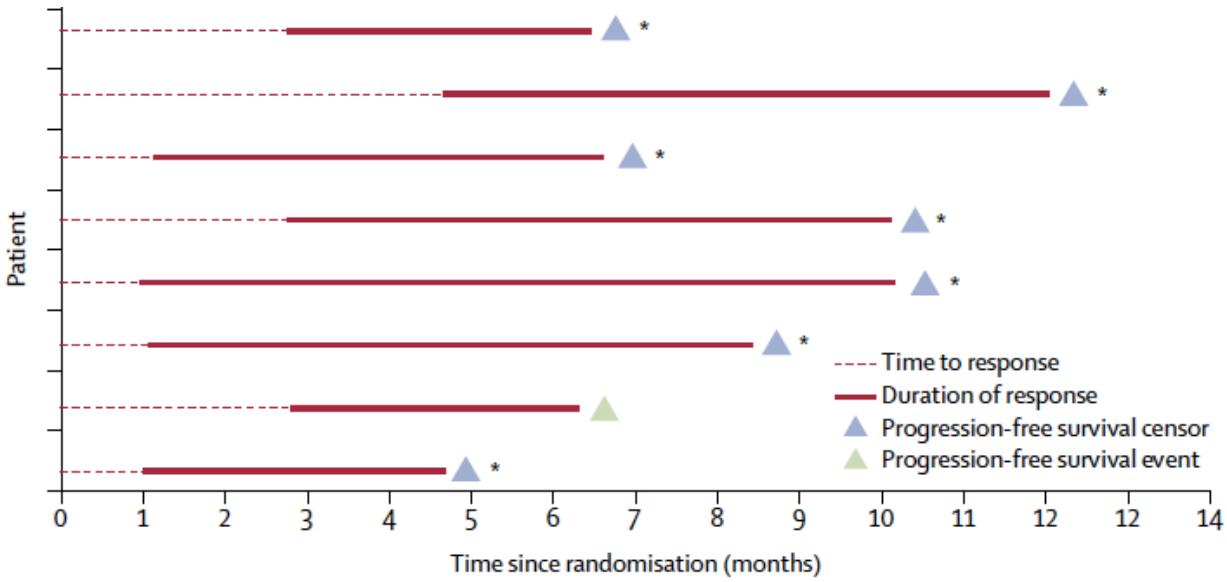
Other secondary endpoints

The secondary endpoints of DOR, TTP, and time to best response were not included in the statistical hierarchy due to insufficient power. There results reported herein are descriptive and are not tested for statistical significance (3).

Responses in patients treated with ripretinib were durable, with median DOR not yet reached at the time of data cut-off (no patients in the placebo group had a response to treatment; Table 12) (3). [redacted]

Median time to best response was 1.9 months (interquartile range [IQR] 1.0 to 2.7) with ripretinib, whereas no patients in the placebo group achieved a response. Median TTP was longer in the ripretinib group (6.4 months [95% CI 4.6 to 8.4]) compared with the placebo group (1.0 month [95% CI 0.9 to 1.7]) (3). [redacted] Time to best response and DOR in the eight responders in the ripretinib group are presented in Figure 10.

Figure 10: Time to best response and DOR in the eight patients in the ripretinib group who responded



Abbrevations: DOR – Duration of response.
* Patient responding at time of data cut-off.
Source: Blay et al. 2020 (3), page 929, figure 3.

HRQoL

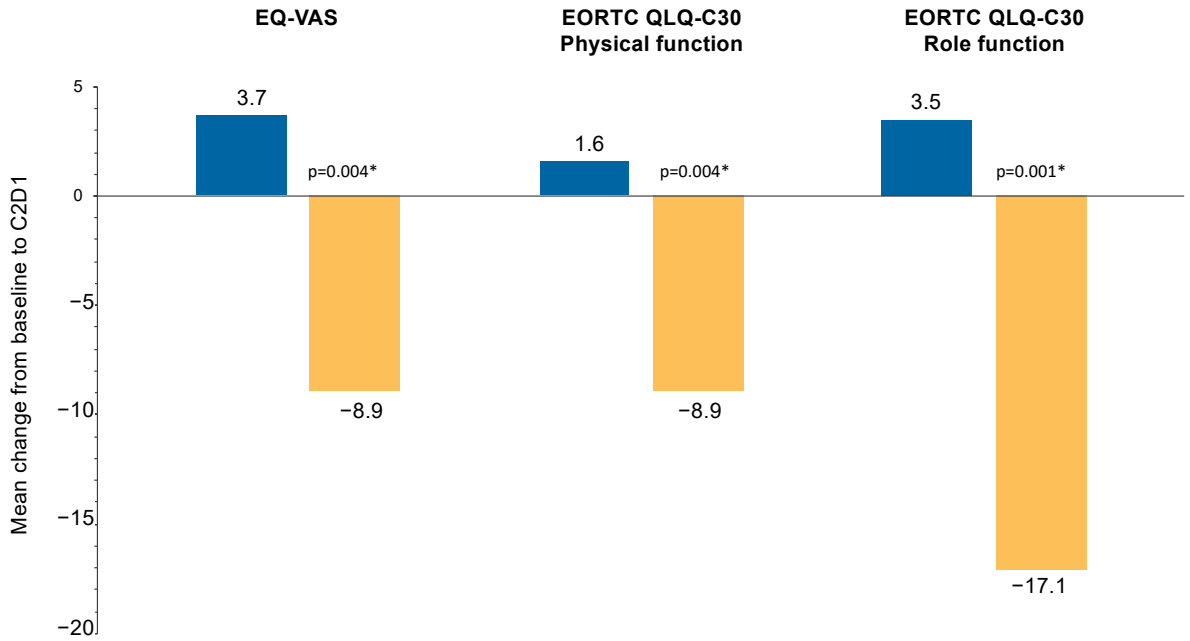
Because ORR did not reach statistical significance, HRQoL results could not be formally tested for statistical significance owing to the hierarchal testing procedures of endpoints (3). Results reported are descriptive and statistical significance is not implied.

HRQoL in INVICTUS was assessed using the EORTC QLQ-C30 role and physical functioning domains, EQ-5D-5L and EQ-VAS from baseline to Cycle 2 Day 1 between the ripretinib and placebo groups. At Cycle 2 Day 1, 71 patients were evaluable in the ripretinib arm and 32 patients were evaluable in the placebo arm. At Cycle 3 Day 1, 61 patients were evaluable in the ripretinib arm and 13 patients were evaluable in the placebo arm. Comparisons were only made up until Cycle 2 Day 1 due to the low number of patients in the placebo group after this time point (61).

Patients in the ripretinib group reported an improvement for the physical and role functioning domains of the EORTC QLQ-C30 from baseline to Cycle 2 Day 1, with an adjusted mean increase in scores (indicating improvement) of 1.6 and 3.5, respectively, compared with a decline of 8.9 and 17.1 for patients in the placebo group (3). 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 differences in patient-repored outcome (PRO) measures between patients receiving ripretinib and those receiving placebo were considered clinically significant (61).

An MCID for HRQoL has not been established in GIST (71). A >10% mean score change or score change of 5 points was considered the threshold to determine a minimally important clinical difference (3). Based on this definition, treatment with ripretinib led to a clinically meaningful benefit compared with placebo across PROMs, as shown by the HRQoL scores presented in Figure 11 and Table 14.

Figure 11: Change from baseline to Cycle 2 Day 1 in EQ-VAS and EORTC QLQ-C30 PROMs (ITT population)



Abbreviations: C2D1 – Cycle 2, day 1; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS – EuroQol visual analogue scale; ITT – Intent-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] (61), figure 3 and Blay et al. 2020 (3), supplementary appendix, table S3.

Table 14: HRQoL scores from baseline to Cycle 2 Day 1 (ITT population)

	Ripretinib (n=85)	Placebo (n=44)
EORTC QLQ-C30*		
Role Functioning		
Baseline, mean (SD; 95% CI)	n=74	n=42
	69.4 (30.1; 62.4 to 76.3)	73.8 (30.4; 64.3 to 83.3)
C2D1, mean (SD; 95% CI)	n=79	n=33
	75.1 (26.1; 69.3 to 81.0)	65.2 (27.8; 55.3 to 75.0)
Change from baseline, adjusted mean (95% CI)	n=70	n=32
	3.5 (-3.4 to 10.5)	-17.1 (-27.0 to -7.1)
Treatment difference (95% CI)	20.6 (8.6 to 32.6)	
Physical Functioning		
Baseline, mean (SD; 95% CI)	n=74	n=42
	75.7 (21.6; 70.7 to 80.7)	76.0 (26.5; 67.8 to 84.3)
C2D1, mean (SD; 95% CI)	n=80	n=33
	79.4 (17.3; 75.5 to 83.3)	75.2 (20.2; 68.0 to 82.3)
Change from baseline, adjusted mean (95% CI)	n=71	n=32
	1.6 (-2.5 to 5.7)	-8.9 (-14.8 to -3.0)
Treatment difference (95% CI)	10.5 (3.4 to 17.6)	
EQ-5D-5L		
EQ-VAS, overall health		
Baseline, mean (SD; 95% CI)	n=74	n=42
	63.9 (22.1; 58.8 to 69.0)	65.6 (22.9; 58.5 to 72.8)
C2D1, mean (SD; 95% CI)	n=78	n=33
	69.5 (20.5; 64.9 to 74.2)	64.1 (23.3; 55.9 to 72.4)
Change from baseline, mean (SD; 95% CI)	n=70	n=32
	3.7 (20.4; -1.1 to 8.6)	-8.9 (19.3; -15.9 to -1.9)

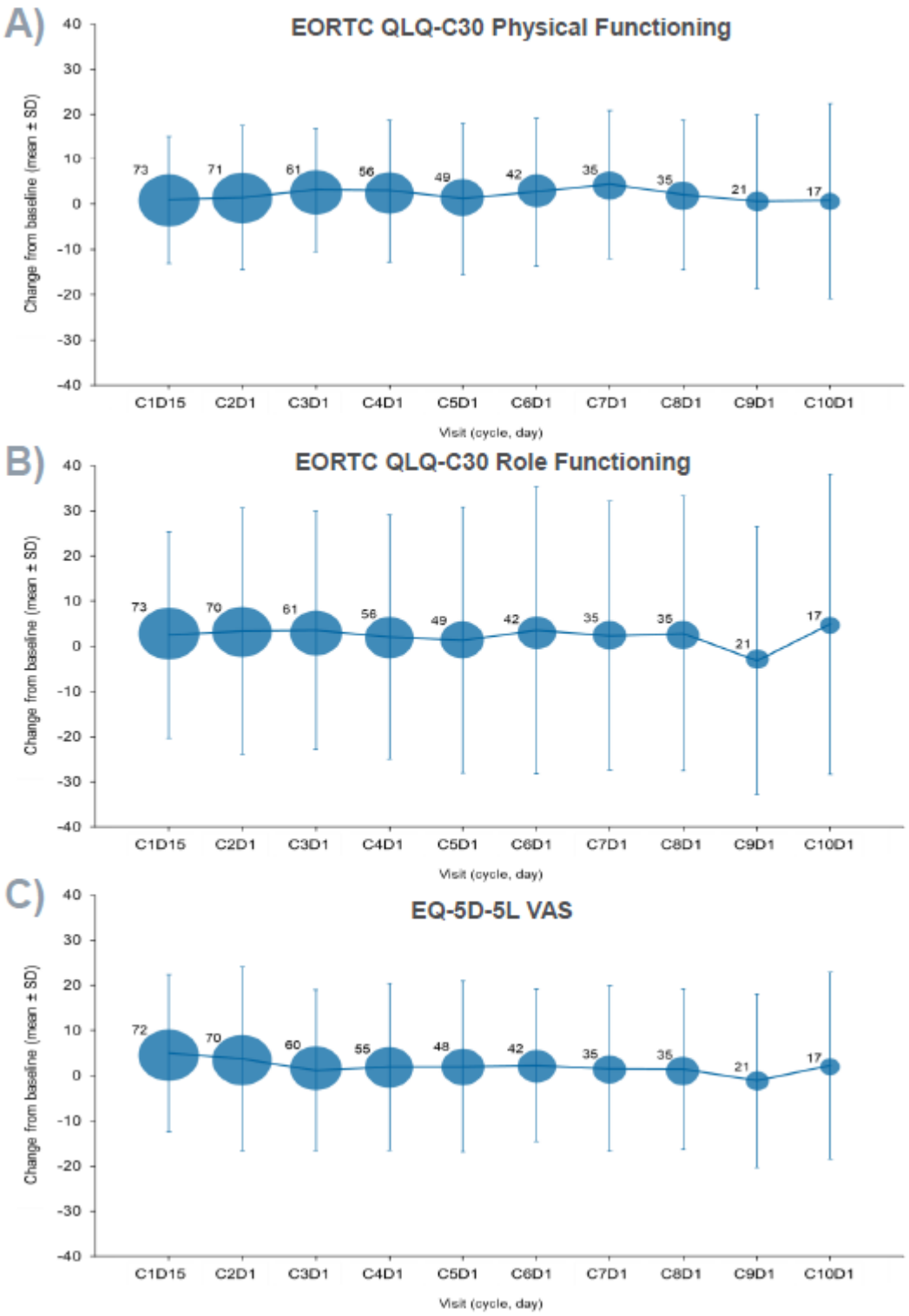
Abbreviations: C2D1 – Cycle, 2 day; CI: Confidence interval; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS – EuroQol visual analogue scale; EQ-5D-5L – EuroQol 5 dimensions 5 levels; HRQoL – Health-related quality-of-life; ITT – Intent-to-treat; SD – Standard deviation.

* Either a >10% mean score change or score change of 5 points was considered the minimally important clinical difference.

Source: Blay et al. 2020 (3), supplementary appendix, table S3.

Longitudinal change in PRO scores from baseline in the ripretinib arm were measured. Patients treated with ripretinib reported a stabilisation in scores for all PRO measures through to Cycle 10, as shown in Figure 12, indicating that these patients were able to maintain quality-of-life and function (61).

Figure 12: Longitudinal change in PRO scores in the ripretinib 150 QD group (ITT population)



Abbreviations: EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-5D-5L VAS – EuroQol 5 dimensions 5 levels visual analogue scale; ITT – Intent-to-treat; PRO – Patient-reported outcome; QD – Once a day.

Note: the size of the blue dot is proportional to number of patients.

Source: Heinrich et al. 2020, poster presented at ASCO [Poster 423] (61), figure 4.

HRQoL was maintained in patients in the ripretinib group experiencing the commonly reported treatment-emergent adverse event (TEAEs) of alopecia or palmar-plantar erythrodysaesthesia syndrome (PPES), reported in 52% and 21% of patients, respectively (66). Scores for role and physical functioning on the EORTC QLQ-C30 and overall health on the EQ-VAS were stable (66).

Time until definitive deterioration

Compared with those receiving placebo, patients receiving ripretinib reported longer TUDD in PRO measures, defined as a clinically meaningful decline in the PRO measure that does not recover (based on a data cut-off of August 2019) (62). This was seen for each of the PRO measures of EQ-VAS, physical and role functioning (jointly measured), overall health, and overall QoL on the EORTC QLQ-C30. Patients in the placebo group reported definitive deterioration within a median of 8 weeks, whereas median TUDD in overall health was not reached in the ripretinib group. For physical and role function (EORTC QLQ-C30) and EQ-VAS scores, TUDD was 41.6 weeks in the ripretinib group. Median TUDD was not shorter than median PFS with ripretinib, suggesting that tolerability did not drive treatment discontinuation (62).

B.2.7 Subgroup analysis

Subgroup analyses were conducted for the primary efficacy endpoint of PFS for the populations listed in B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence. These analyses were pre-specified in the SAP. HR values for each subgroup were calculated using Cox regression with treatment as a fixed factor and the 95% CI of the HR was based on the Wald method (3).

The efficacy of ripretinib in patients dose escalating to ripretinib 150 BID in the open-label period following disease progression was an exploratory endpoint of INVICTUS, which was pre-specified in the SAP (65,70). The “post intra-patient dose escalation” (IDPE) analysis was conducted on the safety population of patients who were treated with ripretinib 150mg BID in the open-label period. PFS1 in the IPDE population was defined as the time from randomisation to disease progression. PFS2 was defined as time from the first dose of ripretinib 150 mg BID to disease progression or death. Both PFS1 and PFS2 were assessed by BICR and analysed using Kaplan-Meier

methodology (65). The same statistical analysis methods used for the ITT population were applied to analyses of the open-label period (70). A post hoc analysis of OS was conducted for the subgroup of patients in the placebo group who crossed over to ripretinib in the open-label period on disease progression (n=29). The survival curves and median OS of the subgroups are based on the Kaplan-Meier method (3).

Results of subgroup analyses for PFS (pre-specified), PFS in the open-label IPDE population (pre-specified) and OS (post hoc) are described in Appendix E.

B.2.8 Meta-analysis

Not applicable. Only one study (INVICTUS) was identified in the SLR as being relevant for inclusion in the submission, and included the only comparator of interest – BSC. Therefore, a meta-analysis has not been conducted.

B.2.9 Indirect and mixed treatment comparisons

Not applicable. Only one study (INVICTUS) was identified in the SLR as being relevant for inclusion in the submission, and included the only comparator of interest – BSC. Therefore, an indirect treatment comparison has not been conducted.

B.2.10 Adverse reactions

Summary of safety

Safety analyses were conducted for the safety population during the double-blind period. The safety population was defined as all patients who received at least one dose of study drug and included all 85 patients randomised to ripretinib 150 mg QD and 43 out of the 44 patients randomised to placebo (128 in total) (3). One patient was randomised to placebo yet did not receive treatment (3).

Ripretinib was generally well-tolerated and associated with an acceptable safety profile in INVICTUS. The overall frequency of TEAEs was similar between the ripretinib and placebo groups (99% vs 98%) (60).

Approximately half of patients in the ripretinib group experienced a grade 3 or 4 TEAE (49%) and 8% experienced a TEAE leading to treatment discontinuation (60). Grade 3 or 4 TEAEs and TEAEs leading to discontinuation were reported in a similar proportion of patients in the placebo group (44% and 12%, respectively). Treatment-

emergent SAEs were reported in 31% and 44% of patients in the ripretinib and placebo groups, respectively (60). Treatment-related TEAEs leading to discontinuation occurred in 5% of patients who received ripretinib as compared to 2% of patients who received placebo (3).

Overall, rates of discontinuation, dose reduction and dose interruption due to adverse reactions were similar between the ripretinib and placebo groups. A summary of TEAEs occurring in INVICTUS is provided in Table 15.

Table 15: Summary of TEAEs in the double-blind phase (safety population)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any TEAE	84 (98.8%)	42 (97.7%)
Any grade 3/4 TEAE	42 (49.4%)	19 (44.2%)
Any treatment-emergent SAE	26 (30.6%)	19 (44.2%)
Any TEAE leading to treatment discontinuation	7 (8.2%)	5 (11.6%)
Any TEAE leading to death	5 (5.9%)	10 (23.3%)
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%)
Any treatment-related TEAE leading to treatment discontinuation	4 (4.7%)	1 (2.3%)
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%)**

Abbreviations: 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 (3), supplementary appendix, table S2; von Mehren et al. 2019, presentation at ESMO (abstract LBA87 and poster) (60).

Death

[redacted] In the ripretinib group, death occurred in 12 out of the 85 patients (14%), of which 11 were due to disease progression and one was of unknown reason (3). Thirteen of the 43 patients in the placebo group (30%) died, of which 11 were due to disease progression and two each separately due to an AE of acute kidney injury and septic shock (3). One treatment-related death occurred in the ripretinib group due to

unknown cause. One treatment-related death occurred in the placebo group due to septic shock and pulmonary oedema (Table 15) (3).

TEAE by type

The most common TEAEs (≥20%) among the 85 GIST patients treated with ripretinib were alopecia (52%), fatigue (42%), nausea (39%), abdominal pain (37%), constipation (34%), myalgia (32%), diarrhoea (28%), decreased appetite (27%), palmar-plantar dysesthesia syndrome (21%), and vomiting (21%) (60). These were mainly grade 1 or 2 in severity.

Grade 3 or 4 TEAEs reported in ≥5% of patients in the ripretinib arm were anaemia (9%), abdominal pain (7%), and hypertension (7%) (60). The most common grade 3 or 4 laboratory abnormalities (≥4%) were anaemia (9%), increased lipase (5%), and hypophosphataemia (5%). Serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anaemia (3.5%), nausea (2.4%), and vomiting (2.4%) (60).

A similar proportion of patients in both groups experienced any grade 3 or 4 event (49% and 44% in the ripretinib and placebo groups, respectively) (60). Table 16 lists TEAEs >10% in the ripretinib group compared to the placebo group (60).

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

TEAE	Ripretinib 150 mg QD any grade (n=85)	Ripretinib 150 mg 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

TEAE	Ripretinib 150 mg QD any grade (n=85)	Ripretinib 150 mg QD grade 3/4 (n=85)†	Placebo any grade (n=43)*	Placebo grade 3/4 (n=43)*†
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

Abbreviations: 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 (60).

Safety findings were consistent with the previous primary analysis results after an additional 9 months of follow-up in the updated analysis (59). In the long-term update of mature data for INVICTUS after an additional 19 months of follow-up, safety findings were consistent with results from the primary analysis (4). The increase in TEAEs and the number of new TEAEs leading to dose modification or death were minimal (Table 17) and the majority of TEAEs were grade 1/2 in severity (4).

Table 17: Summary of TEAEs leading to dose modification

Parameters, n (%)	Ripretinib (n=85)	Placebo (n=43)*
Any TEAE leading to dose interruption	24 (28%)	10 (23%)
Any TEAE leading to dose reduction	8 (9%)	1 (2%)
Any TEAE leading to treatment discontinuation	7 (8%)	5 (12%)
Any TEAE leading to death**	6 (7%)	10 (23%)

Abbreviations: TEAE – Treatment-emergent adverse event.

* 44 patients were randomised to placebo, but one did not receive treatment.

** Three deaths considered possibly related to blinded study drug; two in ripretinib arm and one in placebo arm (due to two events of septic shock and pulmonary edema).

Source: von Mehren et al. 2021, presented at ESMO (4).

B.2.11 Ongoing studies

Table 18 lists the ongoing studies of ripretinib in advanced GIST that may provide additional information of ripretinib in advanced GIST in the next 12 months.

The phase 1 study (NCT02571036) is a first-in-human, non-randomised study of ripretinib, which included patients with advanced GIST and disease progression on at least one systemic anticancer therapy (≥ first-line), including a cohort of advanced ≥4L GIST patients (n=83). It also included patients with other malignancies (72). The study involved two phases: a dose escalation phase, which established the recommended phase 2 dose (RP2D) of ripretinib (150 mg QD) for further evaluation in the expansion phase (68). Results have been reported for the GIST cohorts at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in 2019 [abstract C077] (data cut-off 10 August 2019) and in the Journal of Clinical Oncology in 2020 by Janku et al. 2020 (data cut-off 31 August 2019) (67,68). The Janku et al. 2020 publication reports the most recent data cut. Median PFS was 5.5 months and ORR was 7.2% in the ≥4L GIST cohort, thereby supporting the efficacy of ripretinib in this advanced GIST patient population (68). This study has not been presented in the main body of the submission because this was a phase 1 non-randomised trial of patients with advanced GIST in different lines of therapy.

There is an ongoing double-blind phase 3 RCT assessing the comparative efficacy of ripretinib versus sunitinib in 2L GIST after treatment with imatinib (INTRIGUE) (73,74), and an ongoing phase 2 single-arm open-label study being conducted in China in patients with advanced GIST who have received prior anticancer therapies (NCT04282980) (75). Although results of INTRIGUE are available, the study did not reach its primary endpoint. The results of INTRIGUE are not relevant to this submission in terms of efficacy as the trial was not conducted in the post-regorafenib 4L setting. However, it may provide additional supportive evidence on the efficacy and safety of ripretinib in GIST.

Table 18: Ongoing clinical trials of ripretinib in advanced GIST

Study identifier	Description	Status	Publication
NCT03353753 INVICTUS	Phase 3, randomised, placebo-controlled, double-blind, international,	Active, not recruiting	

Study identifier	Description	Status	Publication
	multicentre study comparing the efficacy of ripretinib to placebo in patients who have received treatment with 3 prior anticancer therapies, including imatinib, sunitinib, and regorafenib.	Estimated completion date April 2022	
NCT03673501 INTRIGUE (73,74)	Phase 3, multicentre, RCT of ripretinib vs sunitinib in advanced GIST following treatment with imatinib (i.e., 2L).	Active, not recruiting Estimated completion date March 2022	Nemunaitis et al., 2020 (clinical trial protocol) (73)
NCT02571036 FIH, phase 1 dose escalation/ expansion study (68,72)	Phase 1, open-label, FIH, single-arm study of ripretinib conducted in 2 phases: a dose escalation phase followed by an expansion phase at the RP2D to assess safety, PK, and preliminary antitumour activity in patients with advanced malignancies, including GIST patients in the ≥1L setting.	Active, not recruiting Estimated completion date June 2022 (results available)	Janku et al., 2020 (68) Chi et al., 2019 (67)
Phase 2 study in China (NCT04282980) (75)	Phase 2, a single-arm, open-label multicentre study conducted in China of patients with advanced GIST who have progressed with prior anticancer therapies.	Active, not recruiting Estimated completion date June 2022	N/A

Abbreviations: GIST – Gastrointestinal stromal tumour; FDA – Food and Drug Administration; FIH – First-in-human; L – line; PK – Pharmacokinetics; RCT – Randomised controlled trial; RP2D – Recommended phase 2 dose.
Sources: as listed in the table.

B.2.12 Innovation

There are no alternative treatment options other than BSC for patients progressing on, or intolerant to, 3L regorafenib in England and Wales, therefore representing a patient population with a high unmet medical need. There is need for broad-spectrum inhibition of the many mutations that fuel resistance and progression in advanced GIST. Ripretinib is a switch control tyrosine kinase inhibitor capable of broadly inhibiting wild type and mutated KIT and PDGFRA (2).

Based on the primary efficacy analysis in the double-blind period of INVICTUS, ripretinib led to a statistically significant and clinically meaningful improvement in median PFS compared with placebo (6.3 vs 1.0 months; p<0.001). Patients achieved a clinically meaningful survival benefit when treated with ripretinib versus patients on placebo. The median OS was 15.1 months in the ripretinib group versus 6.6 months in the placebo group (HR 0.36, 95% CI 0.21 to 0.62). Ripretinib was well-tolerated and

demonstrated an acceptable safety profile. Commonly reported TEAEs (≥20%) with ripretinib were mainly grade 1 or 2 in severity. The favourable efficacy outcomes with ripretinib were supported by maintenance of HRQoL in this advanced population, which was observed regardless of the two commonly reported TEAEs of alopecia and PPES.

The rapid clinical decline seen in patients treated with placebo highlights the urgent need for new treatments and the role for ripretinib as an innovative therapy that has the potential to provide substantial health-related benefits for heavily pre-treated GIST patients who have no other treatment options.

B.2.13 Interpretation of clinical effectiveness and safety evidence

This submission is based on one robust phase 3 randomised, placebo-controlled trial (INVICTUS) of ripretinib compared with placebo in addition to BSC in patients with advanced GIST who have had disease progression or intolerance to prior treatment with ≥3 anticancer therapies. This is in line with the decision problem and scope of the submission. Furthermore, as a multicentre, double-blind, parallel-group, randomised, placebo-controlled trial, the internal validity of the INVICTUS study is high and follows the gold-standard study design for interventional clinical trials.

Results from INVICTUS are relevant to clinical practice in the UK and demonstrate external validity. Patients enrolled were representative of patients with advanced GIST. The overall population was primarily male (57%) with a median age of 60 years old (60). KIT exon 11 mutations were the most common mutation type (58%) (3). This reflects the known epidemiology of GIST in the UK, as reported by Bulusu et al. 2013 (see also section B.1.3 Health condition and position of the technology in the treatment pathway) (34).

Use of ripretinib led to a more than 6-fold increase in median PFS over BSC ($p<0.001$) and led to a median OS improvement of 8.5 months, whilst offering a well-tolerated safety profile and maintenance of HRQoL. Mature long-term data of INVICTUS further support the clinically meaningful benefit in PFS and OS for ripretinib, along with a continued acceptable safety profile in patients with advanced GIST treated with 3 or more prior TKIs. These are highly relevant outcomes for advanced cancer patients, where prolonged survival, manageable toxicities, and maintenance of HRQoL are very

important. Given the numerical improvement in median OS, ripretinib meets the end-of-life criteria by extending life beyond 3 months for patients who have a life expectancy of substantially less than 24 months with BSC – Table 19.

Table 19: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	BSC patients in the INVICTUS trial had a median OS of 6.6 months (3). BSC patients in the two-stage adjustment simple model (treatment switch and time to progression) used in the economic analysis had a median OS of [redacted] weeks.	B.2.6 Clinical effectiveness results of INVICTUS, OS – secondary endpoint, page 40 B.3.3 Clinical parameters and variables page 74
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Compared with BSC, ripretinib extends life by a median of 8.5 months based on the median OS analysis of INVICTUS (15.1 vs 6.6 months) (3). Compared with BSC, in the two-stage adjustment simple model (treatment switch and time to progression) used in the economic analysis, ripretinib extends life by a median of [redacted] weeks based on the median OS analysis of INVICTUS ([redacted] vs [redacted] weeks).	

Abbreviations: BSC – Best supportive care; ECOG PS – Eastern Cooperative Oncology Group Performance Status; NHS – National Health Service; OS – Overall survival; QoL – Quality-of-life.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A three health state partitioned survival model (progression-free disease, progressed disease and death) was developed to evaluate cost-effectiveness of ripretinib compared to BSC in adults with advanced GIST after 3 therapies including imatinib.
- There are currently no lines of pharmacological therapy recommended specifically for the treatment of patients with GIST whose disease has progressed

after treatment with third-line therapy in the UK. It is therefore proposed that the place of ripretinib would be in the fourth-line of treatment.

- Health state-based utilities, patient baseline characteristics and incidence of adverse events were based on data collected in the INVICTUS trial. Cost and resource use estimates were sourced from relevant clinical and economic literature.
- In the ITT data set of INVICTUS, PFS for ripretinib and BSC, and OS for ripretinib were modelled using a standard parametric approach through the fitting of survival data to the observed Kaplan-Meier data from the INVICTUS trial. OS for BSC were adjusted using the two-stage approach to account for the high level of crossover from the placebo arm to the ripretinib arm following disease progression in the trial. The best-fitting curves were selected based on statistical fit and clinical plausibility.
- Ripretinib meets criteria for inclusion into the NICE's End-of-Life category. The life expectancy for the patient population treated with BSC alone is under 24 months and there is sufficient evidence that ripretinib results in greater than 3 months additional survival.
- In the base-case analysis, ripretinib generates [redacted] incremental QALYs and £[redacted] incremental costs over a 40-year horizon compared with BSC, resulting in an incremental cost-effectiveness ratio (ICER) of £[redacted] per QALY gained.
- Results are robust to uncertainty, including probabilistic sensitivity analysis (PSA), one-way sensitivity analysis (OWSA) and scenario analyses. In the probabilistic analysis, the cost per QALY gained is £[redacted] and ripretinib has a [redacted]% chance of being cost-effective at £50,000 per QALY.

B.3.1 Published cost-effectiveness studies

A systematic review of the published literature was conducted to identify economic evaluations assessing the treatment of patients diagnosed with advanced/metastatic or unresectable GIST at any line of therapy. Full details of the search are provided in Appendix G.

For extraction, 23 economic evaluation references (n=23 unique CEA [cost-effective analysis]/CUA [cost-utility analysis] studies) were identified. There were 21 CEAs and

two CUAs extracted, from the perspective of the UK, Canada, the US, Australia, Spain, the Netherlands, Belgium, Germany, Finland, France, Italy, Poland, Turkey, China, Singapore, Brazil, and Mexico. A summary of the economic evaluation studies is provided in Table 20.

Table 20: Summary of economic evaluations identified in the SLR

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
Banerjee et al. (76)	2020	Imatinib, sunitinib, best supportive care	Model Type: Markov; Health States: Imatinib 400mg, Imatinib 800mg, Sunitinib, Best Supportive Care, Disease progression, Death; Cycle Length: 2 months; Perspective: US payer; Horizon: 10 years; Discount Rate: 3% annually for cost and effectiveness	Metastatic GIST	TGT-directed therapy: $478,619 Empirical imatinib: $469,106	QALYs- TGT-directed therapy: 4.98 Empirical imatinib: 4.88	TGT-directed therapy was associated with an ICER of $92,100 per QALY compared with the empirical imatinib approach
Bond et al. (77) TA179	2009	Sunitinib vs placebo	Model Type: Markov model; Health States: (3) progression-free survival, progressive disease, death; Cycle Length: NR; Perspective: NHS and Personal Social Services perspective; Horizon: NR; Discount Rate: NR	Unresectable and/or metastatic GIST after failure of imatinib	NR	NR	Pfizer's base-case analysis: £27,365 per QALY When the cost of the first cycle of treatment was included, using RPSFT effectiveness data: £32,636 per QALY
Centanni et al. (78)	2020	Sunitinib (Fixed dosing) (control) vs TDM-based dosing vs ANC-based dosing vs VEGFR-3-based dosing	Model Type: Simulation frameworks; Health States: NR; Cycle Length: NR; Perspective: NR; Horizon: 5 year; Discount Rate: NR	1,000 virtual individuals with metastatic and/or unresectable GIST	Incremental costs- VEGFR-3 based dosing: €60,783 TDM-based dosing: €59,749 ANC-based dosing: €62,937	Incremental QALYs- VEGFR-3 based dosing: 1.47 TDM-based dosing: 1.22 ANC-based dosing: 1.29	VEGFR-3 based dosing: €36,784 per QALY TDM-based dosing: €173,150 per QALY ANC-based dosing: €104,438 per QALY
Chabot et al. (79)	2008	Sunitinib vs BSC	Model Type: Markov model; Health States: (2) progression-free, progression; Cycle Length: 6 weeks; Perspective: Provincial health ministry	GIST intolerant or resistant to imatinib	Mean cost for sunitinib: CAN$46,125 Mean cost for BSC: CAN$11,632	Mean QALYs for sunitinib: 0.97 Mean QALYs for BSC: 0.54	CAN$79,884 per QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			perspective, Horizon: Lifetime; Discount Rate: 5% on costs and outcomes				
Contreras-Hernandez et al. (80)	2008	Sunitinib vs palliative care vs high doses imatinib	Model Type: Markov model; Health States*: a) (3) Sunitinib treatment (no progression), Palliative care (progression), Death; b) (3) Palliative care (progression), High dose of imatinib (800 mg/day), death; c) (2) Palliative care(with/without progression), death; Cycle Length: NR; Perspective: national health payer in Mexico, the Instituto Mexicano del Seguro Social; Horizon: 5 year; Discount Rate: 5% cost and benefit * (a) Markov model considering sunitinib malate treatment. (b) Markov model considering high doses of imatinib treatment. (c) Markov model considering the palliative treatment	Advanced GIST	Mean cost per patient- Sunitinib malate: US$17,805.87 BSC: US$2,071.86 High doses imatinib: US$35,225.61	Mean LYG- Sunitinib malate: 1.40 BSC: 1.08 High doses imatinib: 1.31	High doses imatinib was dominated vs sunitinib and palliative care for ICER per years gained and ICER per years of free survival progression Palliative care vs sunitinib ICER: US$46,108.89 per years of free survival progression and US$56,612.55 per years gained
Deger et al_a (81)	2015	Regorafenib vs standard care	Model Type: Markov model; Health States: progression-free, progressed, dead; Cycle Length: NR; Perspective: Turkish	Metastatic/inoperable GIST	Total costs- Regorafenib: ₺22,902 Standard care: ₺1,692	QALYs gained- Regorafenib: 2.714 Standard care: 1.402	₺16,481

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Payer Social Security Institution perspective, Horizon: NR; Discount Rate: NR				
El Ouagari et al. (82)	2008	Imatinib vs no treatment	Model Type: NR; Health States: NR; Cycle Length: NR; Perspective: Canadian third-party payer perspective; Horizon: 10 years; Discount Rate: 5% on costs and QALYs	Unresectable/ metastatic GIST	Incremental costs: $80,172	Incremental QALYs: 1.77	$45,284 per QALY
Farid et al. (83)	2020	Continued imatinib until progression (CIUP) vs Surgical resection with upfront abdominoperineal resection (UAPR)	Model Type: Markov; Health States: 12 including UAPR at 1st year ("UAPR_Yr1"), UAPR at 2nd year ("UAPR_Yr2"), UAPR at 3rd year and beyond ("UAPR_Yr3+"), 1st local recurrence following upfront abdominoperineal resection ("Salvage Sx following LR1 post UAPR_Yr3+"), Patients receiving the second strategy ("CIUP"), Patients undergoing abdominoperineal resection following local progression on CIUP ("abdominoperineal resection following LR on CIUP") or subsequently salvage surgery following 1st	Rectal GIST requiring abdominoperineal resection following neoadjuvant imatinib	UAPR: SGD 312,627 CIUP: SGD 339,011	QALYs- UAPR: 8.66 CIUP: 5.43	UAPR is dominating over CIUP.

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			local recurrence after abdominoperineal resection on CIUP ("Salvage Sx following LR1 post CIUP")Distant recurrence ("1st DR"), 1st progression in metastatic disease ("mets disease 1st PD"), 2nd progression in metastatic disease ("mets disease 2nd PD"), 3rd progression in metastatic disease ("mets disease 3rd PD"), death ("Dead"); Cycle Length: 1 year; Perspective: Healthcare payer; Horizon: 20 years; Discount Rate: 3% annually for costs and health outcomes				
Hislop et al. (84)	2011	Imatinib	Model Type: Markov model; Health States: Seven care pathways with BSC, imatinib 600-stable, imatinib 800-stable, sunitinib-stable, progress, failed treatment BSC, death; Cycle Length: 1 month; Perspective: NHS perspective; Horizon: 10 years; Discount Rate: 3.5% on cost and benefit	Unresectable and/or metastatic GIST	Incremental costs- Sunitinib vs BSC: £3,877 Imatinib 600mg vs BSC: £50,372 Imatinib 600mg to sunitinib vs BSC: £2,139 Imatinib 800mg vs BSC: £4,702 Imatinib 800mg to sunitinib vs BSC: £6,628 Imatinib 600mg to imatinib	Incremental QALYs- Sunitinib vs BSC: 0.014 Imatinib 600mg vs BSC: 1.845 Imatinib 600mg to sunitinib vs BSC: 0.030 Imatinib 800mg vs BSC: -0.651 Imatinib 800mg to sunitinib vs BSC: -0.627 Imatinib 600mg to imatinib 800mg to	Sunitinib vs BSC: £272,365 per QALY Imatinib 600mg vs BSC: £27,304 Imatinib 600mg to sunitinib vs BSC: £71,723 per QALY Imatinib 800mg vs BSC: Dominated Imatinib 800mg to sunitinib vs BSC: Dominated Imatinib 600mg to imatinib 800mg to sunitinib vs BSC: £44,359

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
					800mg to sunitinib vs BSC: £22,953	sunitinib vs BSC: 0.517	
Huse et al. (85)	2007	Imatinib mesylate vs no treatment (palliative and supportive care only)	Model Type: cost-effectiveness model (survival model); Health States: (2) alive and on treatment, or alive with progressive disease; Cycle Length: NR; Perspective: US societal perspective; Horizon: 10 years; Discount Rate: 3.0% on future costs and quality-adjusted survival	Advanced GIST	Incremental costs: $74,369	Incremental QALYs: 1.92	$38,723 per QALY
Liao et al. (86)	2021	Ripretinib vs Placebo	Model Type: Markov model; Health States: progression-free, progression, death; Cycle Lengths: 28 days; Perspective: payer; Horizon: Lifetime; Discount Rate: 3% per annum costs and health benefits	Advanced GIST	Total costs for placebo: $189,854. Total costs for ripretinib: $260,105	Total QALYs for placebo: 0.52 Total QALYs for ripretinib: 0.81	$244,010 per QALY gained
Mabasa et al. (87)	2008	Imatinib vs control (historical)	Model Type: NR; Health States: NR; Cycle Length: NR; Perspective: British Columbia Cancer Agency perspective, Horizon: NR; Discount Rate: NR	Advanced GIST	Mean total cost per patient-Imatinib: CAD$79,829 Control: CAD$1,743 Median total cost per patient-Imatinib: CAD$72,523 Control: CAD$0	NR	CAD$15,882 per median LYG CAD$$23,603 per median year of PFS.

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
Nerich et al. (88)	2017	- Strategy 1: 1L imatinib 400 mg/day, without the introduction of imatinib 800 mg/day and sunitinib, followed by best supportive care (BSC). - Strategy 2: 1L imatinib 400 mg/day, followed by 2L imatinib 800 mg/day, without the introduction of sunitinib, followed by BSC - Strategy 3: 1L imatinib 400 mg/day, followed by 2L sunitinib 50 mg/day for 4 consecutive weeks followed by a 2-weeks off period, without the introduction of imatinib 800 mg/day, followed by BSC - Strategy 4: 1L imatinib 400 mg/day, followed by 2L imatinib 800 mg/day + 3L sunitinib 50 mg/day for 4 consecutive weeks followed by a 2-weeks off period, followed by BSC.	Model Type: Markov decision-analysis model; Health States: (5) first-line treatment, second-line treatment, third-line treatment, best supportive care, death; Cycle Length: 3 months; Perspective: French Public Healthcare System perspective; Horizon: lifetime; Discount Rate: 4% on costs and effectiveness	Advanced GIST	Incremental costs- Strategy 2 vs strategy 1: €3,482 Strategy 3 vs strategy 1: €23,736 Strategy 4 vs strategy 1: €18,166	Incremental effectiveness in months- Strategy 2 vs strategy 1: -3.3 Strategy 3 vs strategy 1: 5.9 Strategy 4 vs strategy 1: 0.6)	Strategy 2 vs strategy 1: Dominated Strategy 3 vs strategy 1: €48,277 per LY saved Strategy 4 vs strategy 1: €14,334
Paz-Ares et al. (89)	2008	Sunitinib vs BSC	Model Type: Markov model; Health States: (3) progression-free survival, progression, death; Cycle Length: 42 days; Perspective: Spanish National Health System perspective; Horizon: 6 years after treatment initiation; Discount	Metastatic and/or unresectable GIST after progression or intolerance with imatinib	Mean costs per patient- Sunitinib: €23,259 BSC: €1,622	QALYs- Sunitinib: 1.00 BSC: 0.55	€49,090 per QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Rate: 3.5% on costs and effects				
Pitcher et al. (90) TA488	2016	Regorafenib + BSC vs BSC	Model Type: partitioned survival model; Health States: (3) progression-free, progressed, dead; Cycle Length: NR; Perspective: English NHS; Horizon: lifetime (40 years); Discount Rate: 3.5% on costs and effects	Metastatic/ unresectable GIST	Total cost- Regorafenib: £36,258 BSC: £25,744	QALYs- Regorafenib: 1.717 BSC: 0.969	£34,420 per QALY (using IPE adjustment, base-case)
Ren et al. (91)	2015	Sunitinib 50 mg/day vs Imatinib 600 mg/day, Imatinib 800 mg/day or BSC	Model Type: Markov model; Health States: NR; Cycle Length: NR; Perspective: Third-party payer perspective; Horizon: 5 years; Discount Rate: 3.5% on costs and outcomes	Metastatic and/or unresectable GIST after progression or intolerance with imatinib	Incremental costs- Sunitinib vs imatinib 600 mg: ¥RMB14,750 Sunitinib vs BSC: ¥RMB 106,889	Incremental QALYs- Sunitinib vs imatinib 600 mg: 0.398 Sunitinib vs BSC: 0.836	Sunitinib vs imatinib 600 mg: RMB¥37,023 per QALY Sunitinib vs imatinib 800 mg: Dominant (lower costs and higher QALYs) Sunitinib vs BSC: ¥RMB 127,801 per QALY
Rui et al. (92)	2021	Pazopanib vs. Regorafenib	Model Type: Three-state partitioned survival model; Health States: progression-free, progression and death; Cycle Lengths: NR; Perspective: Health care system; Horizon: 10 years (Lifetime); Discount Rate: NR	Patients who had metastatic or unresectable GISTs, with the previous failure of at least two drugs, including both imatinib and sunitinib.	Incremental cost of pazopanib vs regorafenib= -$10,180	Incremental QALYs of pazopanib vs regorafenib= -0.28 QALYs	ICER of pazopanib vs regorafenib = $36,480 per QALY gained
Sanz-Granda et al. (93)	2015	Regorafenib vs BSC	Model Type: probabilistic cost-utility Markov model; Health States: (3) stable, progression, death;	Unresectable and/or metastatic GIST	Total cost- Regorafenib: €33,256 BSC: €6,546	QALYs- Regorafenib: 1.718 BSC: 1.073	€30,000 per QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			Cycle Length: NR; Perspective: Spanish National Health System perspective; Horizon: lifetime; Discount Rate: 3% on costs and benefits				
Tamoschus et al. (94)	2017	Regorafenib vs Imatinib rechallenge	Model Type: partitioned survival model; Health States: (3) progression-free, progressed disease, death; Cycle Length: 28 days; Perspective: German payer perspective; Horizon: lifetime; Discount Rate: 3.5% on costs and health outcomes	Metastatic and/or unresectable GIST after treatment failure with at least imatinib and sunitinib	Incremental costs: €8,773	Incremental QALYs: 0.415	€21,127 per QALY gained
Teich et al. (95)	2009	Sunitinib vs Imatinib or BSC	Model Type: Markov model; Health States: NR; Cycle Length: 6 weeks; Perspective: Brazilian Public Health Care System perspective (SUS), Horizon: 6 years; Discount Rate: NR	GIST whose tumour continued to progress	Incremental costs for sunitinib vs BSC-US$61,968 (R$86,756)	In comparison with BSC, sunitinib increases LY and PFLY by 0.3 and 0.26 years, respectively	In comparison with imatininb, sunitinib was both more effective, with 0.02 LY and 0.47 PFLY gained, and less costly over 6 years
Wang et al. (96)	2021	Regorafenib + BSC vs Placebo + BSC	Model Type: Partitioned survival model; Health States: 3 states; Cycle Lengths: NR; Perspective: NR; Horizon: Lifetime; Discount Rate: NR	Patients with metastatic or unresectable gastrointestinal stromal tumours in China	Incremental costs for regorafenib + BSC vs placebo + BSC = $18,233	Incremental QALYs for regorafenib + BSC vs placebo + BSC = 0.05 QALYs	ICER for regorafenib + BSC vs placebo + BSC = $394,773/QALY
Wilson et al. (97)	2005	Imatinib vs control	Model Type: state-transition model; Health States: Control group: (2) progressive disease, death;	Unresectable and/or metastatic GIST	Total costs- Imatinib: £47,521 Control: £4,047	QALYs- Imatinib: 4.85 Control: 3.39	According to the modified Novartis model, after 10 years: £29,789 per QALY

Study	Year	Interventions assessed	Summary of model	Patient population	Base-case cost results	Base-case effectiveness results	Base-case ICERs
			imatinib group: (3) imatinib treatment, progressive disease, death; Cycle Length: 4 weeks; Perspective: UK NHS; Horizon: 10 years; Discount Rate: 6% for costs and 1.5% for health benefit				
Zuidema et al. (98)	2019	Imatinib TDM-guided dosing vs imatinib fixed dosing	Model Type: partitioned survival model; Health States: (6) regular dose imatinib progression-free; escalated dose imatinib progression-free; sunitinib progression-free; regorafenib progression-free; BSC; death; Cycle Length: 14 day; Perspective: societal perspective; Horizon: 5 year; Discount Rate: 4% for costs and 1.5% for QALYs	GIST	Incremental cost: €43,481.44	Incremental QALYs: 0.74 Incremental LYs: 0.78	€58,785.70 per QALY €55,744.87 per LYG

Abbreviations: ANC – Absolute change in neutrophil count; BSC – Best supportive care; CAN – Canadian; CIUP − Continued imatinib until progression; CUA – Cost-utility analysis; ECOG – Eastern Cooperative Oncology Group; GIST – Gastrointestinal stromal tumour; ICER – Incremental cost-effectiveness ratio; IPE – Iterative parameter estimation; LY – Life year; LYG – Life year gained; NR – Not recorded; PFLY – Progression-free life year; PFS – Progression-free survival; QALY – Quality-adjusted life years; RPSFT – Rank preserving structural failure time; SGD – Singapore dollar; SLR – Systematic literature review; SUS – Sistema Único de Saúde; TDM – Therapeutic drug monitoring; TGT – Targeted gene testing; UAPR − Surgical resection with upfront abdominoperineal resection; VEGFR-3 – Vascular-endothelial growth factor-3.

B.3.2 Economic analysis

This section describes the company's approach to estimating the cost-effectiveness of ripretinib versus best supportive care (BSC) in the fourth-line setting for patients with advanced GIST after imatinib. Key features of the economic analysis are provided in Table 21. Further details are provided in subsequent sections.

Table 21: Summary of the economic analysis

Aspect	Details	Justification
Patient population	Patients with advanced GIST after 3 therapies including imatinib.	Aligned with the licence of ripretinib and anticipated final NICE scope.
Analytical method	Partitioned survival model.	The choice of modelling approach was informed by the precedent set by the Committee and review group in TA86, TA179 and TA488 (53–55). The chosen approach is consistent with the method used in the majority of advanced cancer appraisals reviewed by NICE.
Model structure	Three health states (progression-free, progressed disease, and death).	A three health state structure is consistent with approaches accepted in previous NICE technology appraisals in oncology and utilises the key primary (PFS) and secondary (OS) endpoints of the INVICTUS trial (58).
Time horizon	40 years	The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared (99). A 40-year time horizon aligns with the regorafenib NICE submission (TA488), the most recent recommended TA in GIST (55). This value is 100 years – baseline age, reflective of a lifetime horizon.
Cycle length	Monthly cycles (28 days).	The chosen cycle period allows the analysis to capture all relevant costs and health benefits and is consistent with approaches accepted in previous NICE appraisals for GIST. A half cycle correction was applied.
Discounting options	Costs and health outcomes at 3.5% per annum.	In line with NICE reference case (99).
Perspective	NHS and PSS.	In line with NICE reference case (99).
Treatment arms within executable model	• Ripretinib • BSC	In line with final NICE scope and treatment in the INVICTUS trial.

Aspect	Details	Justification
Health effects	• Quality-adjusted life years (QALYs) • Life years (LYs)	In line with NICE reference case (99).
Clinical efficacy and safety	Data were sourced from: • INVICTUS trial data • Published clinical evidence • UK population general mortality	The INVICTUS trial is the primary source of evidence of the efficacy and safety of ripretinib in advanced GIST after 3 therapies including imatinib.
Costs and resource use	Data were sourced from: • NHS reference costs 2019/20 v2 for disease management unit costs • A systematic review of published studies • Previous HTA appraisals within GIST • BNF for drug costs	In line with NICE reference case (99).
Utilities	Data were sourced from: • EQ-5D-5L data collected from the INVICTUS trial, mapped onto the EQ-5D-3L using van Hout et al. (2012) (100)	In line with NICE position statement on the EQ-5D-5L (101).

Abbreviations: ERG – Evidence Review Group; EQ-5D-3L – EuroQoL-Five dimensions-Three levels; EQ-5D-5L – EuroQoL-Five dimensions-Five levels; GIST – Gastrointestinal stromal tumour; HTA – Health technology assessment; LY – Life year; NICE – National Institute for Health and Care Excellence; OS – Overall survival; PFS – Progression-free survival; PSS – Personal Social Services; QALY – Quality-adjusted life year.

Patient population

The population entering the CEM (cost-effective model) are adult patients with advanced GIST who have received prior treatment with 3 therapies including imatinib, in line with the NICE (National Institute for Health and Care Excellence) scope, marketing authorisation, and the intent-to-treat (ITT) population of the INVICTUS trial (102). The age at baseline for patients entering the model is 60.1 years and 56.6% of the model baseline population are male In line with the INVICTUS trial (103).

Time horizon

A time horizon of 40 years from the date of starting fourth-line treatment was used in the base-case in line with the NICE reference case (99). This covers the period over

which all important differences in costs or outcomes between ripretinib and BSC would be observed. The impact of varying the time horizon is explored in scenario analyses.

Discounting

The discount rate used in the base-case for both costs and outcomes are 3.5% per annum, as per the NICE reference case. Additional discount rates of 0% and 6% were also considered as scenario analyses.

Perspective

The model adopts a National Health Service and Personal Social Services (NHS/PSS) perspective as recommended by the NICE reference case. This includes resource use and costs associated with treatment (acquisition and administration), health state costs (including pre-treatment, palliative care, monitoring and tests), end-of-life care and AEs.

Model structure

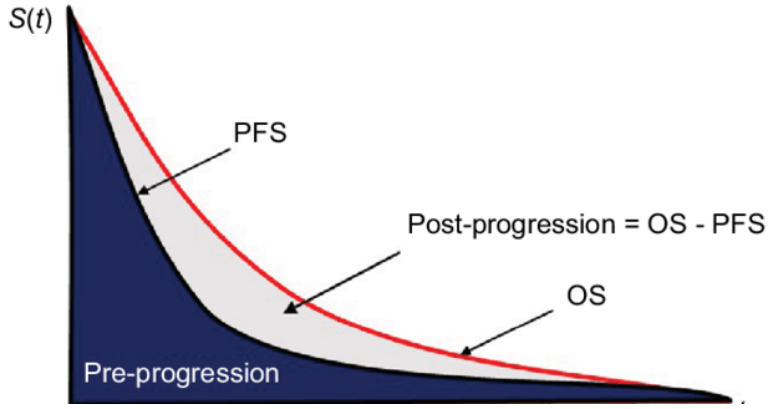
Partitioned survival models (PSMs) have been extensively used to model oncology treatments. In a review by NICE covering the period May 2013-February 2016, it was found that 73% of 30 oncology appraisals appraised by NICE used a PSM (104).

A review of the use of partitioned survival analysis in recent technology appraisals (TAs) of cancer treatments found similar criticisms between the use of PSMs and Markov models. Although the Markov structure allows for more flexibility to model complex disease trajectories, it has additional data requirements than PSMs. In addition, further model structures have been accepted by health technology assessment (HTA), although rarely used, including time in state and cumulative survival.

A PSM structure was selected since the data requirements for partitioned survival analysis are fulfilled by the clinical trial endpoints in INVICTUS. The model was developed in Microsoft Excel®. The model includes three health states: progression-free (PF), progressed disease (PD), and death. In a PSM the distribution of patients between the PF and PD health states over time are estimated based on survival curves. As shown in Figure 13, the OS (overall survival) and PFS (progression-free survival) curves are combined to estimate the proportion of patients PF, with PD and

dead, where S(t) is the probability of survival beyond time t. The area-under-the-curve approach is then used to estimate the time patients spend in the PF and PD states.

Figure 13: Overview of partitioned survival model structure derivation (105)



Abbreviations: OS – Overall survival; PFS – Progression-free survival; S – Probability of survival.

Comparison of chosen methods to previous appraisals

A comparison of methods selected for this appraisal and the approaches adopted in previous GIST appraisals is provided in Table 22. The approaches used in this submission closely match the preferred methods of the committees and review groups in previous relevant GIST appraisals.

Table 22: Comparison of current appraisal to previous relevant published appraisals

Factor	Previous appraisals				Chosen values in current submission	Justification
	TA488	**TA326**	**TA179**	**TA86**		
Population and treatment	Regorafenib – previously treated unresectable or metastatic GIST	Imatinib – adjuvant treatment of GIST	Sunitinib - unresectable and/or metastatic malignant GIST	Imatinib – unresectable and/or metastatic GIST		
Modelling approach	Three health state partitioned survival model	Multi-health state Markov model	Three health state partitioned survival model	Three health state partitioned survival model	Three health state partitioned survival model	Aligns with most recent technology appraisal and the precedent for models in oncology
Time horizon	40 years	50 years	6 years	10 years	40 years	Sufficiently long to capture all the lifetime benefits
Starting age	60 years	61 years	NR	NR	60 years	Average population age in the INVICTUS trial
Half cycle correction	Yes	No	Yes	NR	Yes	Prevents under- or over-estimation of costs and QALYs
Health effects measurement	QALYs	QALYs	QALYs	QALYs	QALYs	NICE reference case

Factor	Previous appraisals				Chosen values in current submission	Justification
	TA488	TA326	TA179	TA86		
Discount rate	3.5%	3.5%	3.5%	6% for costs and 1.5% for QALYs	3.5%	NICE reference case
Perspective (NHS/PSS)	Yes	Yes	Yes	Yes	Yes	NICE reference case
Source of utilities	EQ-5D from trial data	Ara and Brazier (2010), Chabot et al. (2008) and assumptions	EQ-5D from trial data	ECOG performance status mapped to EQ-5D	EQ-5D from trial data	EQ-5D-5L data from the INVICTUS trial mapped to EQ-5D-3L utilities as recommended in the NICE reference case
Source of costs	Bayer, MIMS, NHS reference costs	BNF, NHS reference costs, PSSRU	BNF, NHS reference costs, PSSRU	NR	BNF, NHS reference costs, PSSRU, UK-based published literature	NICE reference case

Abbreviations: ECOG – Eastern Cooperative Oncology Group; EQ-5D – EuroQoL-Five Dimensions; EQ-5D-3L – EuroQoL-Five Dimensions-Three Levels; EQ-5D-5L – EuroQoL-Five Dimensions-Five Levels; GIST – Gastrointestinal stromal tumour; NICE – National Institute for Health and Care Excellence; NR – Not reported; PF – Progression-free; PSS – Personal Social Services; PSSRU – Personal Social Services Research Unit; QALY – Quality-adjusted life year.

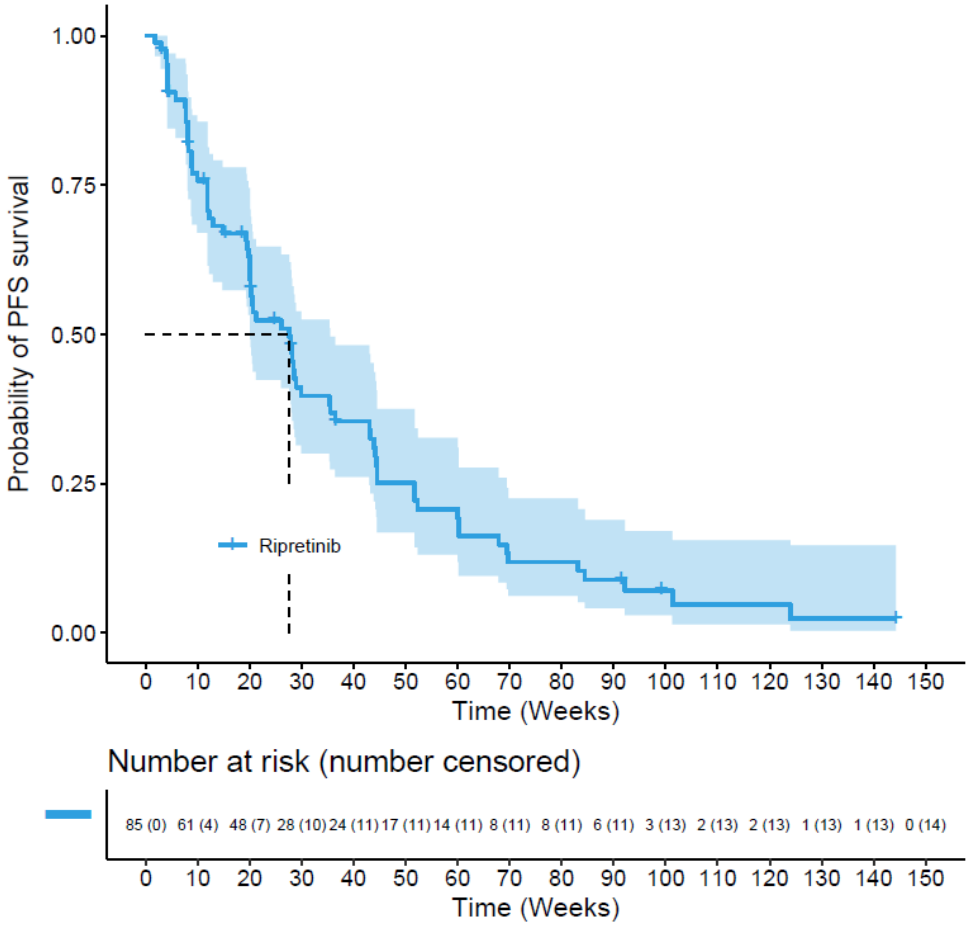
B.3.3 Clinical parameters and variables

Clinical effectiveness parameters are based on data from the INVICTUS study. Survival analysis extrapolation was required to inform state transitions in the model, allowing for evaluation of clinical outcomes over a longer time horizon than that observed in the trial. At the data cut-off of 31 May 2019, the median follow-up time in the double-blind period was 6.3 months (interquartile range [IQR] 3.2 to 8.2) for the ripretinib group and 1.6 months (1.1 to 2.7) for the placebo group (3). Disease progression or death (PFS event) occurred in 60% of patients in the ripretinib group (34 [40%] of patients were censored) and in 84% in the placebo group (seven [16%] patients were censored) (3). From mature OS data for the most recent data cut-off (15 January 2021), 46 (54%) patients in the ripretinib group experienced an OS event (39 [46%] were censored) and 36 (82%) patients in the placebo group experienced an OS event (8 [18%] were censored) (4).

PFS

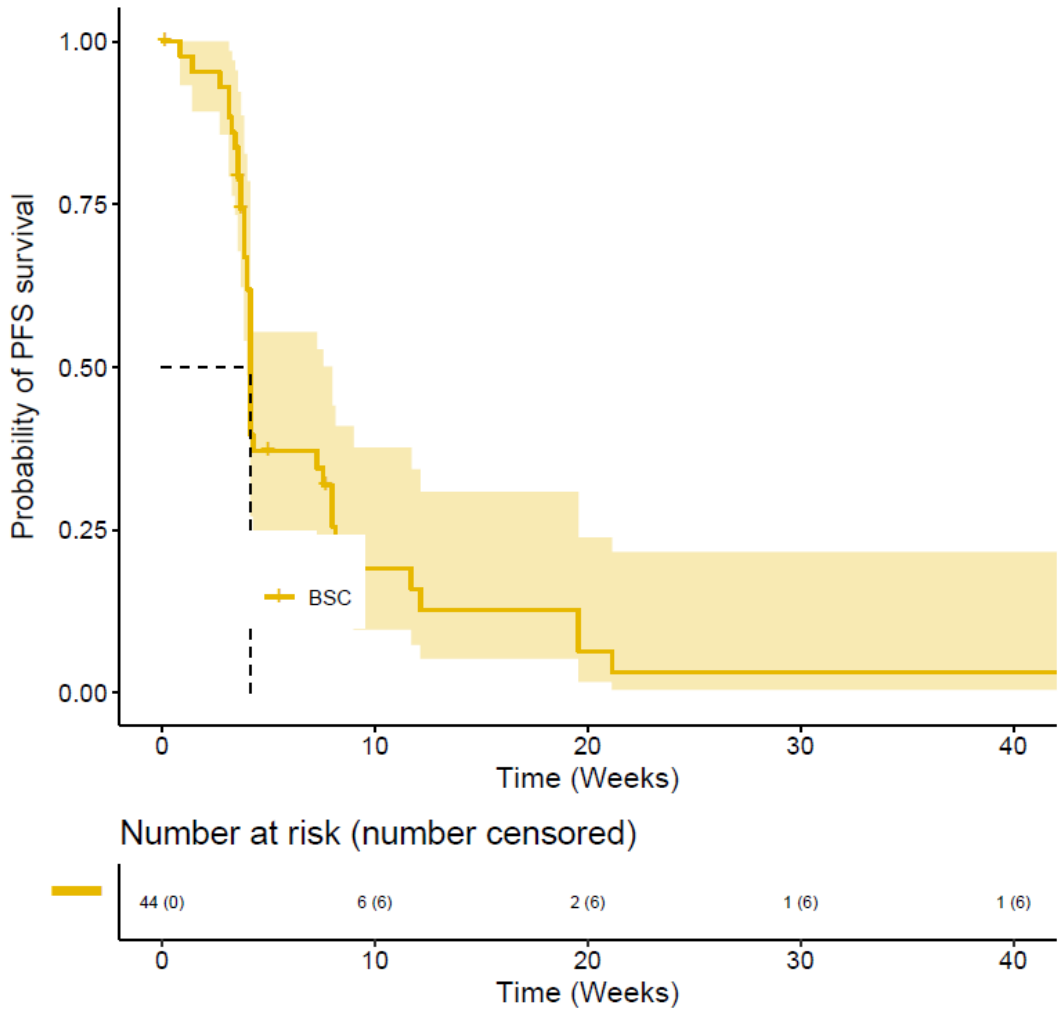
Parametric models were fitted directly to the ripretinib + BSC and BSC (placebo) patient-level data to provide long-term extrapolations. Crossover of patients from the placebo to ripretinib in the INVICTUS trial was only allowed following disease progression, therefore crossover correction was not required for the PFS data. The PFS KM (Kaplan-Meier) curves for ripretinib and BSC from the INVICTUS trial are shown in Figure 14 and Figure 15, respectively. Progression was observed within the trial follow-up period in almost all patients in both arms (77.6% and 84.1% for ripretinib and placebo, respectively).

Figure 14: KM curve PFS ripretinib



Abbreviations: PFS – Progression-free survival.

Figure 15: KM curve PFS BSC



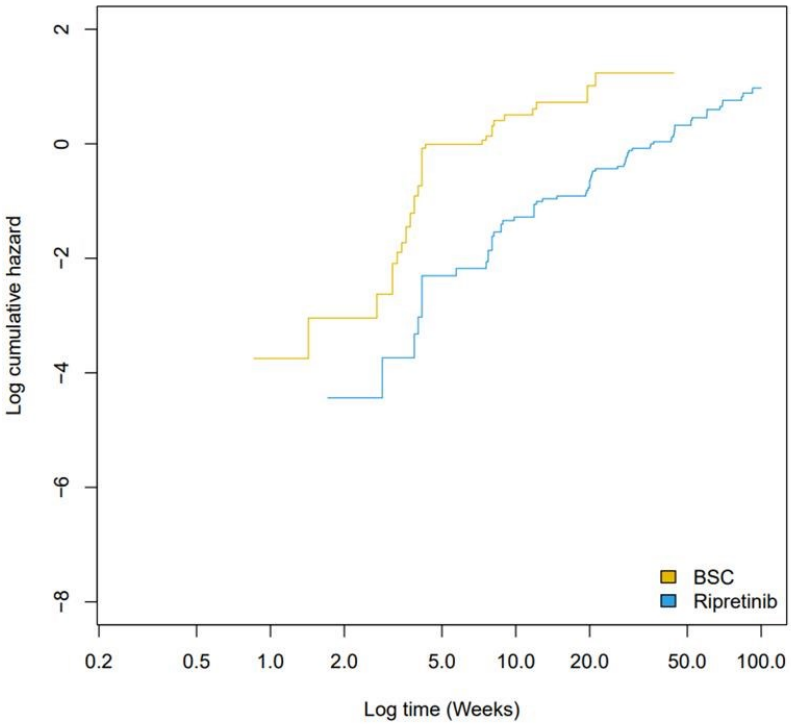
Abbreviations: PFS – Progression-free survival.

Statistical tests were conducted to test if the proportional hazards (PH) assumption holds between the two treatment arms of INVICTUS within the observed trial follow-up period. Two statistical tests were conducted: the complementary log-log plot and the Schoenfeld residuals test. The outcomes of these statistical tests were used to determine whether the null hypothesis, that PH between treatment arms holds, could be rejected.

Inspection of the log-cumulative hazards (Figure 16) and Schoenfeld residual plot (Figure 17) suggests that the relative hazards are likely to vary over time, therefore it is not possible to conclude that the PH assumption holds.

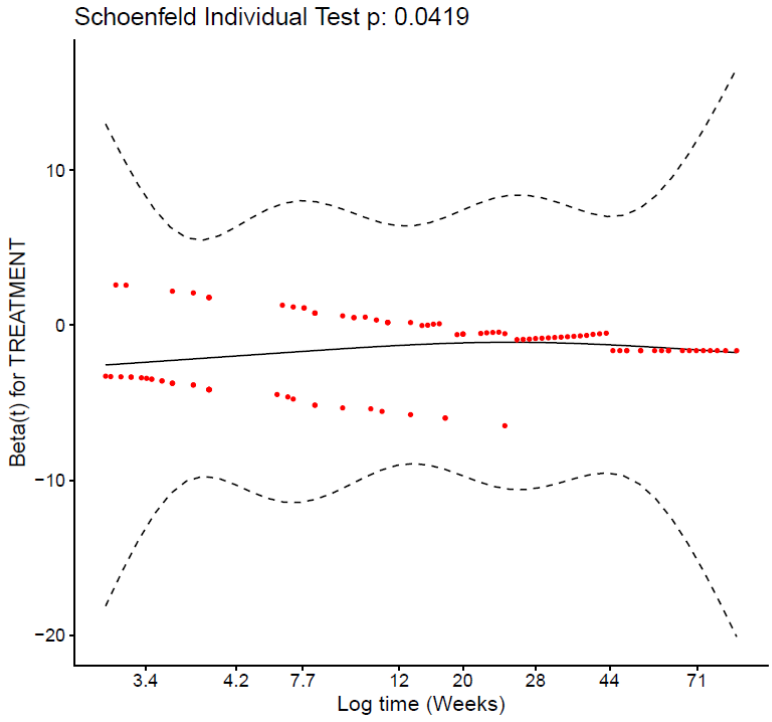
Whilst the lines do not intersect on the log-cumulative hazard plot presented in Figure 16, the respective lines are not strictly parallel. Additionally, the Global Schoenfeld Test is P<0.05, indicating that the PH assumption does not hold.

Figure 16: PFS cumulative log-log plot



Abbreviations: BSC – Best supportive care.

Figure 17: PFS Schoenfeld residuals plot



Given that Figure 16 and Figure 17 demonstrate that the PH assumption does not hold, and patient-level data was available for both arms, six standard parametric independent models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma (Figure 18) . A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 23.

Figure 18: PFS independent parametric curves for ripretinib and BSC

[redacted]

Abbreviations: BSC – Best supportive care; KM – Kaplan-Meier.

Table 23: AIC and BIC statistical goodness-of-fit data for PFS

Distribution	Ripretinib		BSC		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					

Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; BSC – Best supportive care.

The independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period.

However, when fitting curves across two or more treatment groups it is recommended to use the same 'type' of model (for example Weibull for the intervention and the control arms) (106). This allows the two-dimensional treatment effect in the shape and scale parameters to differ between treatment arms but prevents the survival hazards to drastically differ between arms. The combined AICs were calculated, but were too close to be used to make a judgement for the best statistical fit alone. As such, the log-normal distribution was selected as the base-case curve used for PFS extrapolation, based on having one of the lowest combined AICs and best visual fit.

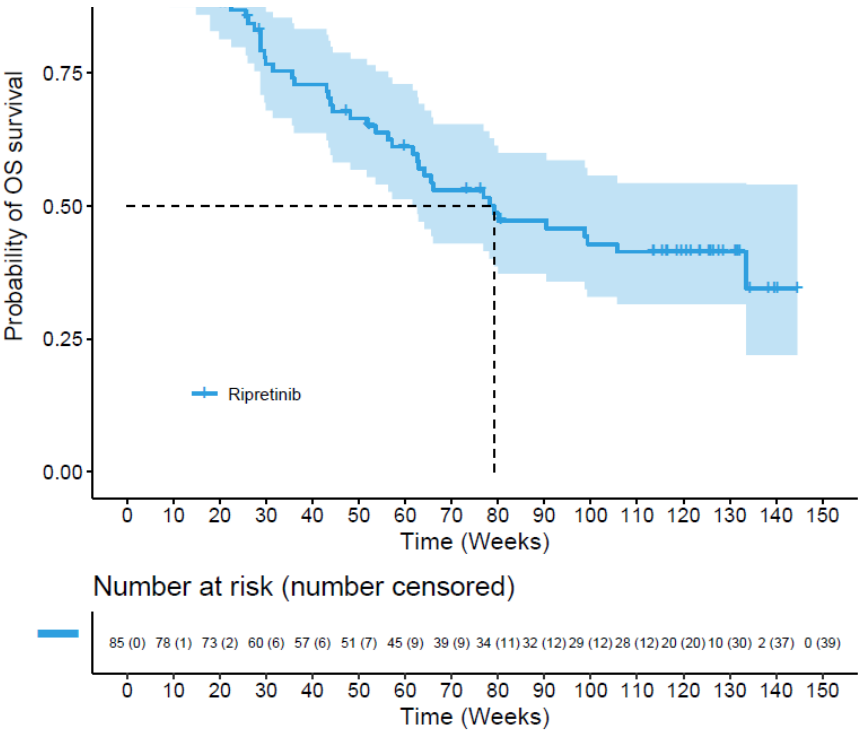
<u>OS</u>

As per the study design for INVICTUS, study drug treatment was unblinded upon disease progression and patients randomised to placebo were given the option to crossover to receive open-label ripretinib.

As the true survival associated with placebo will be confounded by the benefits of crossover onto open-label ripretinib, conventional survival analysis will underestimate the survival benefit associated with ripretinib. Due to the high proportion of patients who crossed over (30/44 patients; 68%), utilising the results of the ITT analysis for OS in the model was deemed inappropriate as the majority of patients in the placebo arm

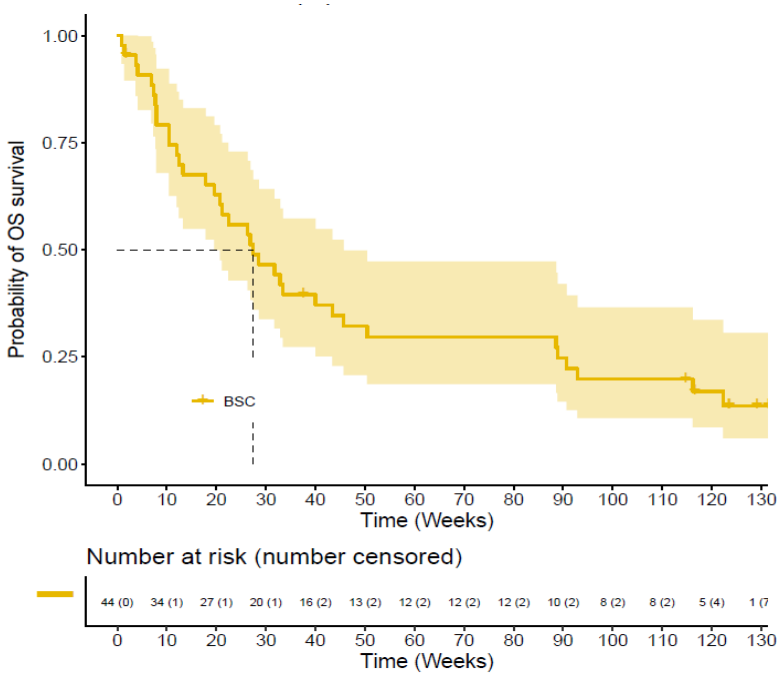
of the trial received ripretinib. The OS KM curves for ripretinib and BSC from the INVICTUS trial are shown in Figure 19 and Figure 20, respectively.

Figure 19: KM curve OS ripretinib



Abbreviations: OS – Overall survival.

Figure 20: KM curve OS BSC



Abbreviations: OS – Overall survival.

Crossover in the INVICTUS trial occurred following disease progression and was therefore non-random. The NICE Decision Support Unit (DSU) recommends the implementation of a variety of potentially appropriate crossover adjustment approaches when adjusting for this high level of crossover, taking into account trial characteristics, the switching mechanism, the treatment effect, and data availability (107). The methods recommended by the DSU include: the two-stage approach, the Inverse Probability of Censoring Weights (IPCW) method and the Rank Preserving Structural Failure Time (RP-SFT) model (107).

The IPCW method was considered but not used due to the small sample size, and the high proportion of placebo patients crossing over to ripretinib treatment (only 14 placebo patients did not enter the open-label trial period), factors responsible for introducing high levels of error in treatment effect estimates (107).

The RPSFTM (rank preserving structural failure time model) method was also considered. This RPSFTM method uses a g-estimation procedure to find the treatment effect, psi (108). The treatment effect is estimated by balancing counterfactual event times across randomised groups (that is, the time that would have been observed if no treatment were received in either randomised group). A key advantage of the RPSFTM method is that the method is randomisation based, and requires only the randomised treatment groups, the observed event times and treatment history in order to estimate counterfactual survival times (108). This method relies on the assumption that the ‘common treatment effect’ exists – that is, the treatment effect received by switchers must be the same (relative to the time the treatment is taken for) as the treatment effect received by patients initially randomised to the experimental group.

The date of first exposure and date of last exposure to ripretinib for each patient was recorded in the trial and was used in the ‘rpsftm’ package in R to obtain the acceleration factor and time ratio associated with ripretinib treatment. The possible test options are the log-rank, and the Wald test from a Cox or Weibull regression model. All three options were explored to derive the acceleration factor (Exp[psi]) and time ratio (Exp[-psi]) associated with ripretinib treatment in the ITT population. The log-rank, Cox and Weibull models all outputted time ratios >15 (Table 24). When

considering the plotted counterfactual survival times shown in Figure 21, the dissimilarity between the curves indicates the g-estimation did not produce a robust outcome. Figure 21 represents the log-rank option but the Cox and Weibull options also outputted very similar results to the log-rank option. Additionally, due to the trial design, whereby patients are only allowed to switch following disease progression, it is unlikely that the 'common treatment effect' assumption holds. As such, the RPSFTM method was ruled out as an option to adjust for crossover but has been explored as part of scenario analysis in the CEM.

Table 24: RPSFTM output

Output	Log-rank	Cox model	Weibull model
Psi (95% CI)	[redacted]	[redacted]	[redacted]
Exp (psi)	[redacted]	[redacted]	[redacted]
Exp (-psi)	[redacted]	[redacted]	[redacted]

Abbreviations: CI – Confidence interval; NA – Not applicable.

Figure 21: Counterfactual event times by treatment arm

Abbreviations: KM – Kaplan-Meier.

The two-stage approach relies on the following assumptions (107):

- A secondary baseline can be defined, at which point patients are at risk of crossover (for example progression).
- No unmeasured confounding at the point of the secondary baseline.
- The RCT (INVICTUS) is appropriately randomised up until the point of disease progression.

Two models were explored, one of which included time to progression as a co-variate (simple model) and another which included the time to progression, Eastern Cooperative Oncology Group performance status (ECOG), QoL (quality of life) and age as co-variates. The following assumptions were made:

- With respect to the time to progression values, 7 of the 44 patients in the placebo group experienced censored progression but continued to be followed up after this. To avoid reducing an already small sample size, it was assumed that the censored time to progression values equated to documented time to progression for these patients.
- ECOG PS and QoL at progression values recorded at the closest time point to progression were used in the analysis.

As time to progression was the only statistically significant co-variate and the use of co-variates in the complex model would add additional uncertainty to the analysis, given the small sample size, the simple model was employed in the base-case analysis. Therefore, the complex model was explored in scenario analyses.

The resulting time ratio was then used to “shrink” the post-progression survival times of switching patients to derive a counterfactual dataset unaffected by switching. Censored progression time was assumed to be equal to documented progression time. The base-case analysis was performed with recensoring to guard against informative censoring (109). Informative censoring occurs when participants are lost to follow-up due to reasons related to the study and can result in biased estimates of treatment effect if not accounted for (109,110). The resulting median OS times for the base-case analysis (simple model) and complex model are presented in Table 25. The adjusted OS BSC base-case KM curve is shown in Figure 22.

Table 25: Median OS times BSC (placebo)

Crossover adjustment method	Median OS BSC (weeks)
Unadjusted	27.43
Two-stage adjustment simple model (treatment switch, time to progression as co-variates)	[redacted]
Two-stage adjustment complex model (treatment switch, time to progression, ECOG PS, age and QoL)	[redacted]

Abbreviations: BSC - Best supportive care; ECOG PS – Eastern Cooperative Oncology Group performance status; OS – Overall survival; QoL – quality of life.

Figure 22: KM curve adjusted OS BSC

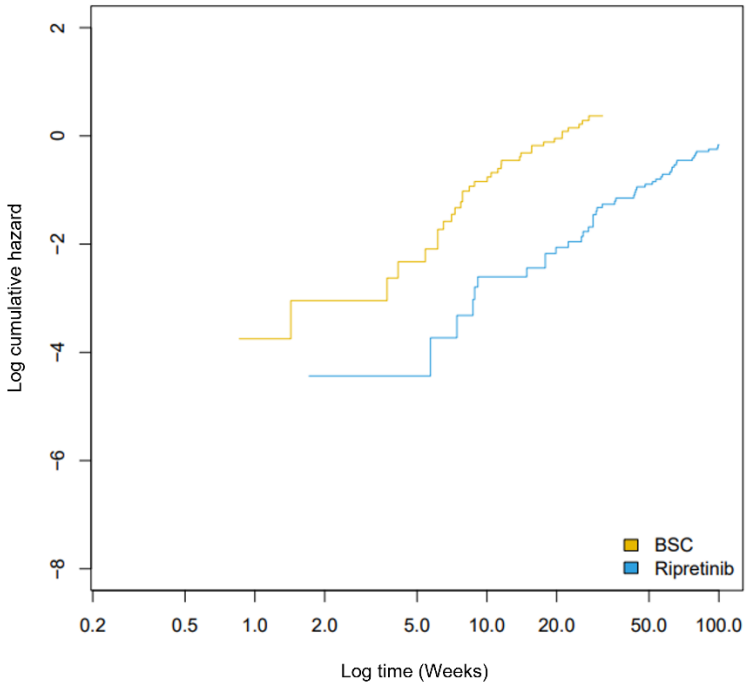
Abbreviations: OS – Overall survival.

Following completion of the cross over adjustment, statistical tests were conducted to test if the PH assumption holds between the two treatment arms of INVICTUS within the observed trial follow-up period. Two statistical tests were conducted: the

complementary log-log plot, and the Schoenfeld residuals test. The outcomes of these statistical tests were used to determine whether the null hypothesis, that is, that PH between treatment arms holds, could be rejected.

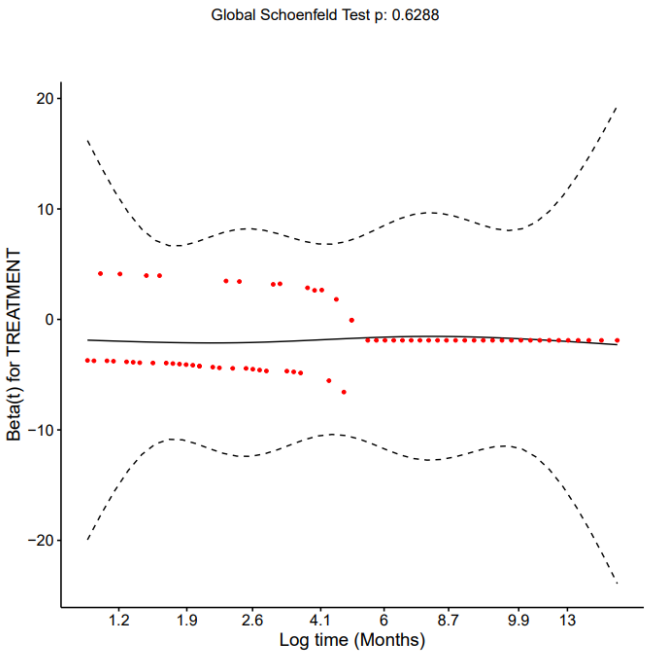
Inspection of the log-cumulative hazards (Figure 23) and Schoenfeld residual plot (Figure 24) suggests that it would be reasonable to accept the PH assumption.

Figure 23: OS cumulative log-log plot



Abbreviations: BSC – Best supportive care.

Figure 24: OS Schoenfeld residuals plot



Whilst the lines do not intersect on the log-cumulative hazard plot presented in Figure 23, the respective lines are not strictly parallel. The Global Schoenfeld Test is P>0.05, indicating that it is not possible to rule out proportional hazards. However, due to the availability of patient-level data, from which counterfactual survival times were derived, six standard parametric independent models were fitted to each arm; exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma (Figure 25). A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table 26**Error! Reference source not found.**.

Figure 25: OS independent parametric curves for ripretinib and BSC

Abbreviations: BSC – Best supportive care; KM – Kaplan-Meier.

Table 26: AIC and BIC statistical goodness-of-fit data for OS

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

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; BSC - Best supportive care.

The independent parametric curves all fitted the data and produced good visual predictions for ripretinib and BSC within the observed period. When fitting curves across two or more treatment groups it is recommended to use the same 'type' of model (for example Weibull for the intervention and the control arms) (106). This allows the two-dimensional treatment effect in the shape and scale parameters to differ between treatment arms but prevents the survival hazards from being drastically different between arms. The combined AICs were calculated, but were too close to be used to make a judgement for the best statistical fit alone. As such, the log-normal distribution was selected as the base-case curve used for OS extrapolation, as having one of the lowest combined AICs and best visual fit.

Background mortality was estimated based on life tables published by the Office of National Statistics (111). Age-dependent background mortality was applied to all non-dead health states to ensure survival did not exceed survival in the general population.

Time to treatment discontinuation (TTD)

Treatment continuation beyond disease progression is not standard clinical practice in England and Wales and ripretinib is not expected to be continued beyond disease progression. As such it was assumed that PFS is equal to time to treatment discontinuation. Compliance and relative dose intensity derived from the double-blind period of the INVICTUS trial was incorporated into the model – see section 3.5. Whilst patients in the ripretinib arm were offered the option to continue ripretinib treatment following progression in the open-label phase, the continued treatment effect beyond progression is unclear. Therefore, the base-case assumes that patients did not continue ripretinib treatment following progression in the open-label phase.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

EQ-5D data were within the INVICTUS trial collected using the EQ-5D-5L instrument. The EQ-5D-5L descriptive system of health states comprises 5 dimensions ('5D'): (1) mobility; (2) self-care; (3) usual activities; (4) pain/discomfort and (5)

anxiety/depression. These are rated by a verbal 5-point rating scale allowing for distinction of five levels ('5L') of severity per dimension and providing a 1-digit number for each dimension: Level 1: no problems; Level 2: slight problems; Level 3: moderate problems; Level 4: severe problems; Level 5: extreme problems. The digits for the 5 dimensions can be combined in a 5-digit code describing the patient's health state. A total of 3,125 different health states are possible (112).

[redacted]

Mapping

The 3-level version (EQ-5D-3L) and the UK time trade-off values set are the reference case for HTA submissions, as defined by NICE. NICE recommend applying the mapping function developed by van Hout et al. (2012) to convert EQ-5D-5L scores to the EQ-5D-3L for the reference case analysis (100). Data was used for the uncensored population only, that is, those who had a documented date of progression. All completed EQ-5D-5L questionnaires that contained responses to all five health domains were mapped to EQ-5D-3L utilities using the crosswalk method by van Hout et al. (2012). Following this, a simple descriptive analysis was conducted on the data to estimate the mean utilities for PF and PD. The results of the EQ-5D analysis are presented in Table 27.

Table 27: EQ-5D-3L values from the INVICTUS trial in the uncensored population

Parameter	Observations (n)	HSUV (SD)
PF	[redacted]	[redacted]
PD	[redacted]	[redacted]

Abbreviations: EQ-5D-3L – EuroQoL-Five Dimensions-Three Levels; HSUV – Health state utility value; PD – Progressed disease; PF – Progression-free; SD – Standard deviation.

Health-related quality-of-life (HRQoL) studies

A systematic review of the published literature was conducted to identify HRQoL of patients diagnosed with advanced/metastatic or unresectable GIST at any line of therapy. The HRQoL SLR (systematic literature review) identified 22 unique references originating from 17 unique studies. Full details of the search are provided in Appendix H.

There were two sources of utility values:

- Values collected from patients directly (involved few studies, which tended to be older studies with small sample sizes and did not provide values for all health states relevant to the metastatic GIST economic models)
- Values mapped from collected HRQoL studies

For extraction, 14 utility value references were identified. A summary of the utility value studies extracted is provided in Table 28.

Table 28: Utility values associated with specific disease states for advanced/metastatic or unresectable GIST

Reference	Population	PF utility value point estimate	PD utility value point estimate	Method of elicitation/valuation
First-line GIST				
Wilson et al. (2005) (97)	Unresectable and/or metastatic GIST (1L)	0.935	0.875	ECOG category mapped to EQ-5D
Second-line GIST				
NICE (sunitinib) (113)	Unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance	0.731[a] 0.781[b]	0.577	Measured EQ-5D
Paz-Ares et al. (2008) (89)	Imatinib-resistant or intolerant metastatic and/or unresectable GIST	0.712[a] 0.781[b]	0.577	Measured EQ-5D
Chabot et al. (2008) (79)	GIST intolerant or resistant to imatinib	0.712[a] 0.781[b]	0.577	Measured EQ-5D
Hislop et al. (2011) (84)	Unresectable and/or metastatic GIST whose disease had progressed on 400 mg/day	-	0.52	ECOG category mapped to EQ-5D
Hislop et al. (2011) (84)	Unresectable and/or metastatic GIST whose disease had progressed on 400 mg/day	0.935[a]	-	Measured EQ-5D
Third-line GIST				
Regorafenib PSD (114)	GIST patients who must have previously failed or be intolerant to imatinib mesylate and sunitinib, must have a WHO performance status of 0	0.767	0.647	Measured EQ-5D

Reference	Population	PF utility value point estimate	PD utility value point estimate	Method of elicitation/valuation
	or 1, and must be aged 18 years or older			
SMC (regorafenib) (115)	Unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib	0.74	0.68	Measured EQ-5D
Zolic et al. (2015) (116)	Metastatic and/or unresectable GIST (3L)	0.872	0.806	Experience based health states (EQ-5D) reported by patients with GIST in the GRID trial combined with utility weights derived from a Swedish population
Zolic et al. (2015) (116)	Metastatic and/or unresectable GIST (3L)	0.850	0.814	Simplest repeated measures model, not including variables for treatment effect
Poole et al. (2015) (38)	Advanced GIST (3L)	0.760[c] 0.767[d]	0.647	Measured EQ-5D
Liao et al. (2021) (86)	Advanced GIST (3L)	0.767	0.647	Measured EQ-5D
Rui et al. (2021) (92)	Advanced GIST (3L)	0.780[e] 0.779[f]	0.647	Measured EQ-5D

Abbreviations: 1L − First-line; 3L − Third-line; EQ-5D – EuroQoL-Five Dimensions; GIST − Gastrointestinal stromal tumour; PSD − Public summary document; SMC – Scottish Medicines Consortium; WHO − World Health Organisation.

[a]Sunitinib

[b]Placebo + BSC

[c]Baseline

[d]On treatment

[e]Pazopanib

[f]Regorafenib

Adverse reactions

Ripretinib was well-tolerated and associated with an acceptable safety profile in INVICTUS. The overall frequency of TEAEs was similar between the ripretinib and placebo groups (99% vs 98%) (60). Safety findings in the January 2021 data cut were consistent with the previous primary analysis results (4).

Approximately half of patients in the ripretinib group experienced a grade 3 or 4 TEAE (49%) with 8% experiencing a TEAE leading to treatment discontinuation (60). Grade 3 or 4 TEAEs and TEAEs leading to discontinuation were reported in a similar proportion of patients in the placebo group (44% and 12%, respectively). Table 29 details the grade 3 or 4 TEAEs that occurred in ≥5% of patients in either treatment arm and were included in the model.

Table 29: Grade 3-4 TEAEs in ≥5% of patients in the ripretinib group compared to placebo

TEAE	Ripretinib 150 mg QD any grade (n=85)	Ripretinib 150 mg QD grade 3/4 (n=85)†	Placebo any grade (n=43)*	Placebo grade 3/4 (n=43)*†
Anaemia	16 (18.8%)	9 (10.6%)	8 (18.6%)	6 (14.0%)
Abdominal pain	34 (40.0%)	6 (7.1%)	13 (30.2%)	2 (4.7%)
Hypertension	13 (15.3%)	6 (7.1%)	2 (4.7%)	0

Abbreviations: QD – Once a day; TEAE – Treatment-emergent adverse event.
* 44 patients were randomised to placebo, but 1 did not receive treatment
† Corresponding grade 3/4 TEAEs to TEAEs in ≥15% of patients receiving ripretinib
Source: von Mehren et al. 2021, slide 15 (presented at ESMO, September 16-21, 2021) (4)

Disutility values specific to patients with GIST for the AEs included above in Table 29 could not be identified in literature searches. Disutility values for AEs were identified in a previous NICE submission for GIST (TA0523) and a NICE submission for colorectal cancer (TA439: review of TA176 and partial review TA240) (6,117). Disutility values for abdominal pain and hypertension originated from Doyle et al. (2008), in the context of advanced non-small cell lung cancer (118). The disutility for abdominal pain was assumed equal to chest pain. The disutility for anaemia originated from Harrow et al. (2011), scaled to EQ-5D, as reported in Hoyle et al. (2013) (119,120). The incidence of the AEs in each arm was multiplied by disutility values to obtain a total AE decrement for ripretinib and for BSC. Disutility of AEs is per event only and not

related to duration of AE impact. All AEs were assumed to occur in the first cycle of the model and are summarised in

Table 30 and Table 31.

Table 30: Ripretinib AE disutility

Adverse event	Disutility	Probability	Total disutility
Anaemia	0.085	0.106	0.0080
Abdominal pain	0.069	0.071	0.0049
Hypertension	0.069	0.071	0.0049
Total			**0.0188**

Table 31: BSC AE disutility

Adverse event	Disutility	Probability	Total disutility
Anaemia	0.085	0.14	0.0119
Abdominal pain	0.069	0.047	0.0032
Hypertension	0.069	0	0
Total			**0.0151**

Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of base-case utility values for the cost-effectiveness analyses is presented in Table 32.

Table 32: Summary of base-case utility values for cost-effectiveness analysis

State	Utility value: mean (SD)	Reference in submission (section and page number)	Justification
PF	[redacted]	Health-related quality-of-life data from clinical trials, page 88	In line with the NICE reference case and reflective of the patient population considered in this submission
PD	[redacted]	Health-related quality-of-life data from clinical trials, page 88	
Grade 3-4 AEs			
Anaemia	-0.085	Adverse reactions, page 93	Identified through targeted published literature search or assumed equivalent to published estimate for a similar AE
Abdominal pain	-0.069	Adverse reactions, page 93	
Hypertension	-0.069	Adverse reactions, page 93	

Abbreviations: AE – Adverse event; NICE – National Institute for Health and Care Excellence; PD – Progressed disease; PF – Progression-free; SD – Standard deviation.

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

A SLR was conducted to identify cost and resource use data associated with the treatment of patients diagnosed with advanced/metastatic or unresectable GIST at any line of therapy. No UK-based studies were identified. See Appendix I for extended detail of how cost and resource use data were reviewed and identified.

The costs included in the model consist of:

1. Treatment-related costs
    - Acquisition costs
    - Administration costs
2. Health state costs
    - Pre-treatment costs
    - Palliative care costs
    - Monitoring and test costs
3. Adverse event costs
4. End-of-life costs

Intervention and comparator costs and resource use

Drug related costs considered include the acquisition and administration cost of ripretinib + BSC and BSC only.

Drug acquisition costs

Ripretinib

Ripretinib is available in 50 mg capsules and the list price per 30-day supply is £18,400. A confidential PAS discount will been submitted in the form of a simple discunt. As the PAS has not yet been submitted, it has not been applied in the model and the results presented do not reflect this discount.

[redacted]

BSC costs were calculated from NICE TA488 (for regorafenib) – see BSC costs and Table 33 below.

BSC

BSC costs were calculated from NICE TA488 (for regorafenib), the most recent recommended TA in GIST, for which a clinician survey was conducted to estimate the proportion of patients treated with pain medication. These physicians were based in England and Wales, therefore these BSC costs are assumed to be more appropriate to the UK setting than those approximated from the concomitant medications taken in the BSC arm of the international INVICTUS trial. Pain management costs were used across both arms (ripretinib and BSC). Dosing as per TA10523/TA488 was combined with costs from the BNF and is presented in Table 33 (6,55,122).The assumed dose for each of the medications was based on their respective SmPC maintenance doses for the most common indication. In instances where the maintenance dose was a range, the lowest maintenance dose was assumed in order to

remain conservative. If the maintenance dose was not stated, half of the maximum dose was assumed. Prescription Cost Analysis data (123) was used to determine the most commonly prescribed dosage form for each medication for costing purposes.

Calculated BSC costs per 28-day cycle are presented in Table 33 A scenario was explored where BSC costs were approximated from the concomitant medications taken in the BSC arm of the international INVICTUS trial (103), with dosing and costs retrieved from the BNF (122). The costs for this scenario are presented in Table 33**: Pain management costs as per TA10523/TA488**

Drug, dose	% patients (PF)	% patients (PD)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (PF)	Cost per 28-day cycle (PD)
Co-codamol, 2 tablets (30/500mg) QDS	18.0%	22.0%	30/500mg tablet	100	£4.00	224	£1.61	£1.97
Tramadol capsules, 100mg QDS	12.0%	14.0%	50mg capsule	100	£2.73	224	£0.73	£0.86
Paracetamol tablets, 1g QDS	33.0%	38.0%	500mg tablet	32	£0.76	224	£1.76	£2.02
Morphine sulfate immediate release tablets, 30mg every 4 hours	20.0%	29.0%	10mg tablet	56	£5.31	168	£3.19	£4.62
			20mg tablet	56	£10.61	168	£6.37	£9.23
Dexamethasone, 4mg OD	11%	19%	4mg tablet	28	£60.01	28	£3.70	£6.39
						Total	**£17.35**	**£25.08**

Abbreviations: NICE – National Institute for Health and Care Excellence; OD – once daily; PD – Progressed disease; PF – Progression-free; QDS – four times a day; TA – Technology appraisal.

Table 34.

Table 33: Pain management costs as per TA10523/TA488

Drug, dose	% patients (PF)	% patients (PD)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (PF)	Cost per 28-day cycle (PD)
Co-codamol, 2 tablets (30/500mg) QDS	18.0%	22.0%	30/500mg tablet	100	£4.00	224	£1.61	£1.97
Tramadol capsules, 100mg QDS	12.0%	14.0%	50mg capsule	100	£2.73	224	£0.73	£0.86
Paracetamol tablets, 1g QDS	33.0%	38.0%	500mg tablet	32	£0.76	224	£1.76	£2.02
Morphine sulfate immediate release tablets, 30mg every 4 hours	20.0%	29.0%	10mg tablet	56	£5.31	168	£3.19	£4.62
			20mg tablet	56	£10.61	168	£6.37	£9.23
Dexamethasone, 4mg OD	11%	19%	4mg tablet	28	£60.01	28	£3.70	£6.39
						Total	**£17.35**	**£25.08**

Abbreviations: NICE – National Institute for Health and Care Excellence; OD – once daily; PD – Progressed disease; PF – Progression-free; QDS – four times a day; TA – Technology appraisal.

Table 34: Concomitant medications across ripretinib and BSC arms used in the base-case

Drug, dose	% patients (BSC)	% patients (ripretinib)	Unit	Units per pack (N)	Cost per pack	Units per cycle	Cost per 28-day cycle (BSC)	Cost per 28-day cycle (ripretinib)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
						Total	**£101.42**	**£92.69**

Abbreviation: BD – twice a day; BSC – Best supportive care; IU – international units; IV – intravenous; m/r – modified release; OD – once a day; QDS – four times a day; TDS – three times a day.

Administration costs

The analysis assumes there is no administration cost for ripretinib+BSC (oral treatment), or BSC only. The only BSC medication that requires intravenous infusion is sodium chloride, for which a single dose is assumed per cycle in the scenario analysis, and only received by 11.6% and 16.5% of patients in the BSC only arm and ripretinib + BSC arm, respectively. The impact of inclusion would be negligible and has been assumed to be zero.

Health state unit costs and resource use

The approach to health state costs was based on TA10523 and TA488 (6,55). The resource use frequencies were based on a survey conducted in 2013 involving 15 physicians from England and Wales. These frequencies were revalidated in 2016 by two consultant oncologists based on the clinical practice in England at the time of the submission.

Table 35 gives the one-off costs of tests taken by a proportion of patients before treatment in addition to palliative surgical resection and palliative radiotherapy given to relieve or prevent symptoms. It is assumed that all patients require regular resource use and regular resource use per patient – monitoring and tests, is reported in Table 36.

The ripretinib marketing authorisation is independent of mutational status, therefore no additional diagnostic testing is expected. According to UK clinical practice, all GIST patients are routinely tested for mutations on diagnosis (5,6). Therefore costs associated with diagnostic testing have not been included in the model.

Table 35: One-off health state resource use

Resource	Unit cost	Mean proportion of patients		Source
		PF	PD	
CT scan	£111.98	Ripretinib: 85% BSC: 24%	-	NICE TA488 (55); NHS reference costs 2019/20 v2 (weighted average of CT scan of three areas, with contrast, RD26Z) (124)
MRI scan	£150.77	Ripretinib: 12 % BSC: 1%	-	NICE TA488 (55); NHS reference costs 2019/20 v2 (weighted average of MRI codes RD01A to RD07Z) (124)
Full blood count	£2.56	Ripretinib: 92% BSC: 56%	-	NICE TA488 (55); NHS reference costs 2019/20 v2 (haematology DAPS05) (124)
Liver function test	£1.20	Ripretinib: 92% BSC: 49%	-	NICE TA488 (55); NHS reference costs 2019/20 v2 (clinical biochemistry DAPS04) (124)
Palliative resection	£3,893.52	10%	10%	NICE TA488 (55); (PD assumed to be same as PF); NHS reference costs 2019/20 v2 (weighted average of costs of malignant gastrointestinal tract disorders with single intervention: FD11D, FD11E, FD11F) (124)
Palliative radiotherapy	£182.87	20%	20%	NICE TA488 (55); (progressed assumed to be same as PFS); NHS reference costs 2019/20 v2 (weighted average of adult medical specialist palliative care attendance costs: SD01A, SD02A, SD03A, SD04A) (124)

Abbreviations: BSC – Best supportive care; GI – Gastrointestinal tract; NICE – National Institute for Health and Care Excellence; PD – Progressed disease; PF – Progression-free; SE – Standard error; TA – Technology appraisal.

Table 36: Regular resource use per patient - monitoring and tests

Resource	Unit cost	PF		PD		Source
		Mean number of weeks between tests	Frequency per 28-day cycle	Mean number of weeks between tests	Frequency per 28-day cycle	
CT scan	£111.98	Ripretinib: 12.1 BSC: 18.9	Ripretinib: 0.33 BSC: 0.21	14.5	0.28	NICE TA488 (55); NHS reference costs 2019/20 v2 (weighted average of CT scan of three areas, with contrast, RD26Z) (124)
MRI scan	£150.77	Ripretinib: 19.9 BSC: 18.0	Ripretinib: 0.20 BSC: 0.22	8.0	0.50	NICE TA488 (55); NHS reference costs 2019/20 v2 (weighted average of MRI codes RD01A to RD07Z) (124)
Full blood count	£2.56	Ripretinib: 6.4 BSC: 10.9	Ripretinib: 0.63 BSC: 0.37	8.8	0.45	NICE TA488 (55); NHS reference costs 2019/20 v2 (haematology DAPS05) (124)
Liver function test	£1.20	Ripretinib: 6.4 BSC: 11.2	Ripretinib: 0.63 BSC: 0.36	9.4	0.43	NICE TA488 (55); NHS reference costs 2019/20 v2 (clinical biochemistry DAPS04) (124)
Outpatient care visit	£200.20	Ripretinib: 6.2 BSC: 7.9	Ripretinib: 0.65 BSC: 0.51	6.9	0.58	NICE TA488 (frequency from patients on BSC) (55); NHS reference costs 2019/20 v2 (WF01A code 370 WF01A Consultant led non-admitted face-to-face attendance, follow-up) (124)

Abbreviations: BSC – Best supportive care; NICE – National Institute for Health and Care Excellence; PD – Progressed disease; PF – Progression-free; TA – Technology appraisal.

Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the evaluation and modelled via the incidence of grade 3-4 AEs. Grade 3-4 AEs occurring ≥5% in either treatment arm were included in the evaluation as they are likely to be associated with costs that will affect decision making. Costs were sourced from the 2019/20 NHS reference costs version 2 (124). Treatment-related grade 3-4 AE rates were obtained directly from the INVICTUS trial.

Table 29 presents the AE rates applied in the model. The base-case costs associated with treating and managing AEs used in the model are presented in Table 37.

Table 37: Cost of resolving AEs in the economic model

Grade 3-4 AE	NHS reference cost 2019/20 v2	NHS currency code description
Anaemia	£762.29	Weighted average of SA01G:SA01K, SA03G:SA03H, SA04H:SA04L and SA05G:SA05J – total HRGs (124)
Abdominal pain	£649.11	Weighted average of FD05A and FD05B – total HRGs (124)
Hypertension	£638.81	EB04Z – total HRGs (124)

Abbreviations: AE – Adverse event; HRG – Healthcare resource group.

End-of-life unit costs and resource use

The approach to end-of-life costs was aligned to TA10523 and TA488 (6,55). The introduction of end-of-life costs does not affect the undiscounted model outcomes as the model effectively has a lifetime time horizon. All patients have died in both arms by the time horizon so the total undiscounted cost associated with end-of-life care is identical in each arm. However, the cost associated with end-of-life care is relevant to discounted model outcomes when mortality differs between arms, since a larger proportion of end-of-life costs are incurred later in the arm with lower mortality. To capture this, end-of-life costs were incorporated into the cost-effectiveness model (6). End-of-life costs were taken from NICE TA488 and inflated to 2020/21 prices using

the HCHS/NHSCII indices (55,125,126). The original cost is taken from a study conducted by Abel et al. (2013) that presents end-of-life costs for a cohort of hospice patients in South West England (127). All patients had a life limiting disease and were referred to the hospice for specialist palliative care. The resulting weighted cost for end-of-life care of £9,635 in Table 38 was allocated to each patient upon death.

Table 38: Base-case end-of-life cost

Detail on end-of-life	% of patients	Cost, inflated to 2020/21
Death in hospital	16%	£13,099.67
Death outside of hospital	84%	£8,961.89
Weighted total		£9,634.90

In line with advice from NICE, a scenario is included using estimates for end-of-life costs from Round et al. (2015) (128). The terminal care costing study incorporated Bayesian modelling using data from the literature and publicly available datasets. Four types of cancer were considered: breast, colorectal, lung and prostate. The cost used within the cost-effectiveness model scenario analysis considers the direct costs borne by the health and social care sectors, in line with the perspective recommended in the NICE reference case. The resulting cost for end-of-life care of £6,858.20 in Table 39 was allocated to each patient upon death.

Table 39: Scenario analysis end-of-life cost

Detail on end-of-life	Mean cost, inflated to 2020/21
End-of-life cost healthcare	£4,796.12
End-of-life cost social care	£2,062.08
Total	£6,858.20

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 40.

Table 40: Summary of variables applied in the economic model

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Lower bound	Upper bound		
Model setup					
Time horizon, years	40	N/A – varied in scenario analyses		N/A	Page 68
Age, years	60.1	N/A	N/A	N/A	
Percentage male	56.6%	34.0%	77.8%	Beta	
Discount rate costs	3.5%	N/A – varied in scenario analyses		N/A	
Discount rate outcomes	3.5%	N/A – varied in scenario analyses		N/A	
Clinical inputs					
Ripretinib - PFS	Log-normal	N/A – varied in scenario analyses		Log-normal	Page 74
Ripretinib - OS	Log-normal	N/A – varied in scenario analyses		Log-normal	
Ripretinib - TTD	Fixed equal to PFS	N/A – varied in scenario analyses		Log-normal	
BSC - PFS	Log-normal	N/A – varied in scenario analyses		Log-normal	
BSC - OS	Log-normal	N/A – varied in scenario analyses		Log-normal	
BSC - TTD	Fixed equal to PFS	N/A – varied in scenario analyses		Log-normal	
Cost inputs					
Ripretinib pre-treatment cost (£)	116.73	75.54	166.74	Gamma	Page 102
BSC pre-treatment cost (£)	30.40	19.67	43.43	Gamma	
Ripretinib cost per cycle (£)	17,173.33	N/A	N/A	N/A	Page 96
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC cost per cycle (ripretinib arm) PF (£)	17.35	11.23	24.78	Gamma	Page 97
BSC cost per cycle (ripretinib arm) PD (£)	25.08	16.23	35.83	Gamma	
BSC cost per cycle PF (£)	17.35	11.23	24.78	Gamma	
BSC cost per cycle PD (£)	25.08	16.23	35.83	Gamma	
BSC compliance	100%	N/A	N/A	N/A	
BSC relative dose intensity	100%	N/A	N/A	N/A	
Ripretinib PF health state total cost (£)	198.83	128.67	284.01	Gamma	Page 103

Parameter	Value	OWSA		Within PSA varied by	Reference to location in submission
		Lower bound	Upper bound		
Ripretinib PD health state total cost (£)	224.00	144.96	319.97	Gamma	Page 103
BSC PF health state total cost (£)	159.93	103.50	228.45	Gamma	
BSC PD health state total cost (£)	224.00	144.96	319.97	Gamma	
Ripretinib palliative care cost PF (£)	425.93	275.64	608.39	Gamma	
Ripretinib palliative care cost PD (£)	425.93	275.64	608.39	Gamma	
BSC palliative care cost PF (£)	425.93	275.64	608.39	Gamma	
BSC palliative care cost PD (£)	425.93	275.64	608.39	Gamma	
End of life cost (£)	9,634.90	6,235.20	13,762.53	Gamma	Page 104
Ripretinib AE total cost (£)	172.25	111.47	246.04	Gamma	Page 104
BSC AE total cost (£)	137.23	88.81	196.02	Gamma	
Utility values					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Page 89
Ripretinib AE total disutility	0.02	0.01	0.03	Beta	Page 94
BSC AE total disutility	0.02	0.01	0.02	Beta	

Abbreviations: AE – Adverse event; BSC – Best supportive care; N/A – Not applicable; OWSA – One-way sensitivity analysis; PD – Progressed disease; PF – Progression-free survival; PSA – Probabilistic sensitivity analysis.

Assumptions

A summary of modelling assumptions is provided, divided by aspect of the cost-effectiveness model, in Table 41.

Table 41: Model assumptions

Category	Assumption	Justification
Population and comparators	The INVICTUS trial is representative of patient population receiving ripretinib and BSC for patients in the UK population who have received prior treatment with three or more kinase inhibitor inhibitors, including imatinib.	In line with anticipated marketing authorisation and NICE scope. Additionally, there were 10 UK patients in the INVICTUS trial (7.75%).
	BSC is an appropriate comparator for ripretinib	BSC (placebo) was the comparator in the INVICTUS clinical trial and is in line with the NICE scope.
Model structure and settings	Partitioned survival model	Reflective of the natural history of the disease and a well-accepted model structure in oncology.
	UK NHS and PSS perspective	In line with NICE reference case.
	Lifetime horizon	In line with the NICE reference and with previous NICE appraisals in GIST.
	3.5% per annum discount rate for costs and outcomes	In line with NICE reference case.
	Half cycle correction applied	Assuming a cost or outcome is incurred on average mid-way through a cycle.
Clinical effectiveness	Two-stage approach provides an appropriate method to account for trial crossover	Patients only able to crossover following disease progression, confounders measured at or close to time of progression, trial randomised up until progression.
	The log-normal distribution provides an appropriate PFS extrapolation	Best visual fit, and one of the best statistical fit.
	Patients discontinue treatment with ripretinib upon disease progression	Treatment continuation beyond disease progression is not standard practice in England and Wales and ripretinib is not expected to be continued beyond disease progression.
	The log-normal distribution provides an appropriate OS extrapolation	Best visual fit, and one of the best statistical fit.
	Grade 3-4 AEs are included and assumed occur in the first cycle of the model time horizon.	AE are likely to occur very soon after treatment and only require acute care. This is consistent to the modelling approaches

Category	Assumption	Justification
		adopted in several oncology TAs for example TA429 and TA561 (129,130).
Cost and resource use inputs	No administration costs for ripretinib	Oral treatments.
	No subsequent lines of therapy, with only BSC costs applied following progression	Ripretinib is expected to be the last line of therapy in UK clinical practice.
	No indirect costs are applied in the model.	In line with the NICE reference case.

Abbreviations: AE – Adverse event; BSC – Best supportive care; GIST – Gastrointestinal stromal tumour; NICE– National Institute for Health and Care Excellence; PSS – Personal social services; TA – Technology appraisal

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

Total costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost per QALY gained for ripretinib versus BSC are presented in Table 42. In the base-case analysis, ripretinib generates [redacted] incremental QALYs and [redacted] incremental costs over a 40-year time horizon compared with BSC, resulting in an ICER (incremental cost-effectiveness ratio) of £[redacted] per QALY gained. Disaggregated base-case results are presented in Appendix J.

Table 42: Base-case results for ripretinib versus BSC

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) were conducted to explore the impact of model parameter uncertainty on the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. Ten thousand simulations were performed, which combined give a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results. PFS and OS remained independent within the PSA as per a standard PSM. However, the sum of the proportion of patients in each health state was not able to exceed 100% of the patient population. For gender proportions, event rates, compliance, relative dose intensity and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs, a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed.

Total costs, QALYs and incremental cost per QALY gained for ripretinib versus BSC are presented in Table 43. An incremental cost-effectiveness plane scatter plot, cost-effectiveness acceptability curve, and cost-effectiveness acceptability frontier were produced to graphically illustrate the level of variability and uncertainty in the results, as shown in Figure 26, Figure 27 and Figure 28, respectively.

Table 43: PSA results for ripretinib versus BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; QALYs – Quality-adjusted life years.

Figure 26: Incremental cost-effectiveness plane for ripretinib versus BSC

Figure 27: Cost-effectiveness acceptability curve for ripretinib versus BSC

Figure 28: Cost-effectiveness acceptability frontier for ripretinib versus BSC

Deterministic sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results. The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed. The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% confidence interval (CI), the high value is the upper bound of the 95% CI. In the absence of CI data, the variable was altered by +/- 20%. A tornado diagram was developed to graphically present the parameters which have the greatest effect on the ICER.

An OWSA diagram presenting the top 15 most sensitive parameters is presented in Figure 29, with tabulated results presented in Table 44. The model was most sensitive to the shape and scale of the ripretinib OS distributions, the shape and scale of the ripretinib PFS distribution, the shape and scale of the BSC OS distributions, the ripretinib health states costs, and the PD utility values.

Figure 29: OWSA tornado diagram

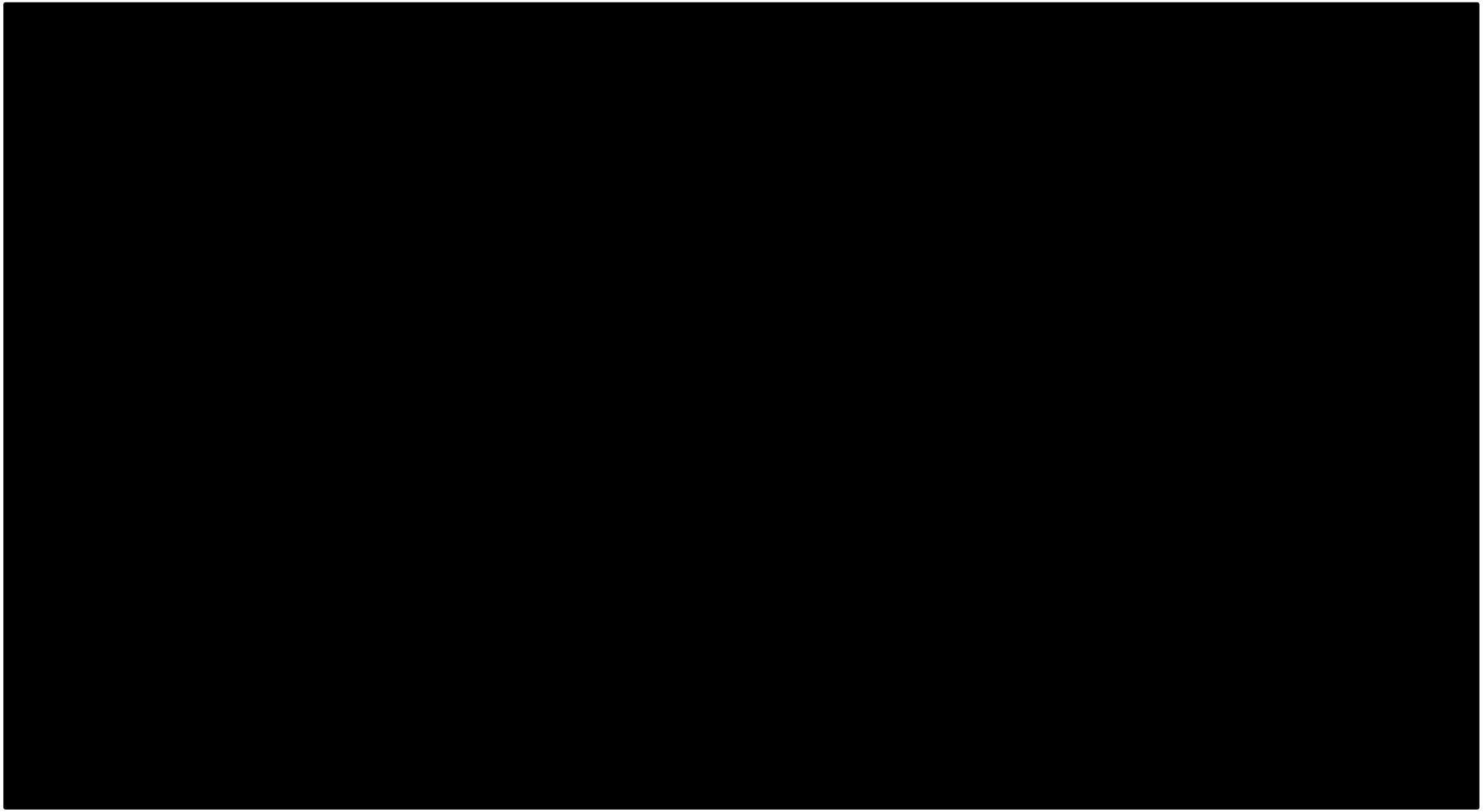


Table 44: Tabulated OWSA results

Parameter	Lower bound ICER	Upper bound ICER	Difference
Ripretinib - OS	[redacted]	[redacted]	[redacted]
Ripretinib - PFS	[redacted]	[redacted]	[redacted]
BSC - OS	[redacted]	[redacted]	[redacted]
Ripretinib PD health state total cost (£)	[redacted]	[redacted]	[redacted]
Utility: PD	[redacted]	[redacted]	[redacted]
Ripretinib relative dose intensity	[redacted]	[redacted]	[redacted]
Ripretinib compliance	[redacted]	[redacted]	[redacted]
Ripretinib PF health state total cost (£)	[redacted]	[redacted]	[redacted]
Utility: PF	[redacted]	[redacted]	[redacted]
BSC cost per cycle (ripretinib arm) PD (£)	[redacted]	[redacted]	[redacted]
BSC PD health state total cost (£)	[redacted]	[redacted]	[redacted]
BSC PF health state total cost (£)	[redacted]	[redacted]	[redacted]
Ripretinib palliative care cost PF (£)	[redacted]	[redacted]	[redacted]
BSC palliative care cost PF (£)	[redacted]	[redacted]	[redacted]
BSC palliative care cost PD (£)	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; OS – Overall survival; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival.

Scenario analysis

Table 45 details the scenario analyses results for ripretinib versus BSC.

Table 45: Scenario analyses for ripretinib versus BSC

Category	Base-case	Scenario	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£)
Base-case			[redacted]	[redacted]	[redacted]	[redacted]
Discount rate	3.5%	0.0%	[redacted]	[redacted]	[redacted]	[redacted]
		1.5%	[redacted]	[redacted]	[redacted]	[redacted]
		6.0%	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	40 years	10 years	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	[redacted]	[redacted]	[redacted]	[redacted]
		30 years	[redacted]	[redacted]	[redacted]	[redacted]
PFS	Log-normal	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
OS	Log-normal	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Category	Base-case	Scenario	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£)
Base-case			[redacted]	[redacted]	[redacted]	[redacted]
Crossover method	Simple two-stage with recensoring	Complex two-stage without recensoring	[redacted]	[redacted]	[redacted]	[redacted]
		Complex two-stage with recensoring	[redacted]	[redacted]	[redacted]	[redacted]
		Simple two-stage without recensoring	[redacted]	[redacted]	[redacted]	[redacted]
		RPSFTM with recensoring	[redacted]	[redacted]	[redacted]	[redacted]
		RPSFTM without recensoring	[redacted]	[redacted]	[redacted]	[redacted]
Ripretinib post-progression adjustment	Unadjusted	Simple two-stage with recensoring	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life cost	TA488 (55)	Round et al	[redacted]	[redacted]	[redacted]	[redacted]
BSC costs	TA488 (55) (clinician survey)	INVICTUS trial	[redacted]	[redacted]	[redacted]	[redacted]
PF and PD utilities	PF=[redacted] PD=[redacted]	TA488 (55) (PF=0.767, PD=0.647)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYs – Life years; OS – Overall survival; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival.

Summary of sensitivity analyses results

Mean PSA results lay close to the deterministic base-case results, and ripretinib was [redacted] cost-effective at a willingness to pay of £50,000 per QALY or more. This threshold has been selected due to ripretinib meeting the end-of-life criteria by extending life beyond 3 months for patients who have a life expectancy of substantially less than 24 months. The cost-effectiveness plane showed similar robustness of results, with point estimates providing a relatively tight spread around the means PSA ICER.

Within the OWSA, all ICERs remained below [redacted] per QALY gained. The model was most sensitive to OS and PFS in the ripretinib group and OS in the BSC group, the total health state cost for PD in the ripretinib group, and the PD utility.

Scenario analyses demonstrated that ripretinib becomes more cost-effective as the time horizon increases, likely due to the tail of the OS extrapolated distributions. Alternative survival curves were also explored as part of scenario analyses. It was shown that the ICER is not particularly sensitive to the choice of curve. A range of crossover adjustment methods were explored, all producing similar results to the base-case analysis. The adjustment of ripretinib OS for patients who continued treatment in the open-label period had a considerable impact on ICER, however, whether continued treatment beyond progression confers any benefit is unclear, and so this adjustment is likely to underestimate the cost-effectiveness of ripretinib.

B.3.9 Subgroup analysis

Patients with advanced GIST who have had at least 3 prior therapies or have documented intolerance to any of these treatments already comprise a small population with high unmet needs. As such, further categorisation by subgroup has not been performed.

B.3.10 Validation

Validation of cost-effectiveness analysis

A two-stage quality control (QC) process was used during the development of the cost-effectiveness model. The first QC occurs after an empty shell model has been constructed with dummy placeholder data. This QC is intended to test the structure of the model, that core calculations such as background mortality are mechanically sound, and that there are no naming errors or common excel errors present. The second QC process occurs at model completion when the model is put through a number of ‘zero tests’, whereby key variables are set to zero and results checked for face validity. The entire model also undergoes a second structural test to ensure all calculations and formulae are correct, followed by a final face validity check to ensure that the context in which the variables are used is clinically and theoretically sound. The process of QC is conducted by an experienced modeller who is not the original model builder, who records their findings against a QC checklist. This document is passed to the original modelling team who must action the recommendations of the

QC modeller, recording their agreements and disagreements in the same document. Where disagreements existed, the project director acted as a third-party and resolved with consensus.

INVICTUS is the longest available data set for patients treated with ripretinib; thus, external validation of the intervention arm for the extrapolations has not been possible. Although data from other studies in advanced GIST are available (for example the A618-1004 [sunitinib] and GRID [regorafenib] studies) these trials were in earlier lines of therapy and do not include ripretinib treatment arms to validate the extrapolation.

To validate the analysis, the median PFS (ripretinib and BSC) and OS (ripretinib) predicted by the model were compared against data in the INVICTUS study (January 2021 data cut), as shown in Table 46. Predicted landmark survival rates compared to the INVICTUS trial (January 2021 data cut) trial KM curve are presented in Table 47. The comparison demonstrates that the model closely predicts the clinical data for ripretinib and BSC.

Table 46: Summary of model predicted outcomes compared with INVICTUS trial data, ITT population

Outcome	Clinical trial result, median weeks	Model result, median weeks
Ripretinib		
PFS	27.57	[redacted]
OS	[redacted]	[redacted]
BSC		
PFS	4.14	[redacted]

Abbreviations: BSC – Best supportive care; OS – Overall survival; PFS – Progression-free survival.

Table 47: Summary of model predicted landmark rates compared with clinical data, ITT population

Distribution	Weeks				
	26	**52**	**78**	**104**	**130**
Ripretinib					
PFS KM data	51%	22%	12%	5%	2%
PFS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS KM data	84%	65%	52%	43%	41%
OS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	13	**26**	**39**	**52**	**65**

BSC					
PFS KM data	13%	3%	3%	N/A	N/A
PFS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; KM – Kaplan-Meier; N/A – Not applicable; OS – Overall survival; PFS – Progression-free survival.

Opinion from an expert in crossover adjustment was sought to identify the most appropriate method to adjust for patients crossing over, following disease progression, from the placebo (BSC) arm to the ripretinib arm. It was deemed that the two-stage approach method, using the time of progression as the secondary baseline, was potentially the most appropriate one to adjust for crossover. The expert in crossover also assisted with technicalities associated with implementation of the crossover adjustments.

B.3.11 Interpretation and conclusions of economic evidence

In current clinical practice in England, no active treatment is available for patients with advanced GIST after 3 therapies. Ripretinib presents an active fourth-line treatment option for patients with a life expectancy of less than 24 months and extends life expectancy by at least 3 months compared to BSC. Ripretinib therefore meets the criteria to be classified as an end-of-life therapy.

Ripretinib was not found to be a cost-effective treatment for patients with advanced GIST who have had at least 3 prior therapies or have documented intolerance to any of these treatments. The base-case analysis resulted in an ICER of [redacted]. A simple PAS discount on the list price of ripretinib will be submitted, which is not reflected in this analysis.

Limitations to the model include the direct applicability of ITT clinical data to inform clinical parameters in the cost-effective analysis. Due to the high proportion of crossover from the placebo arm to the ripretinib arm following progression, the ITT OS data for placebo overestimates the survival associated with BSC. However, statistical correction methods have been presented in line with the NICE DSU recommendations (107), with the two-stage method chosen as the most clinically robust to account for crossover.

Patients in the INVICTUS clinical trial were able to continue treatment with ripretinib following progression. Whilst ripretinib is not expected to be reimbursed beyond progression in the UK, it is unclear whether continued treatment beyond progression with ripretinib confers any benefit. As such, ITT data was used directly to model OS for ripretinib patients, with a scenario analysis conducted to account for continuation beyond progression.

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B.5 Appendices

Please see separate Appendices file uploaded to NICE docs.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

6th June 2022

File name	Version	Contains confidential information	Date
ID3805 ripretinib clarification letter to PM for company AIC _24Jun22_v1.0.docx	**1.0**	**Yes**	**24/06/22**

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Mechanism of action

A1. Company submission (CS), Section B.1.2, page 12. How does ripretinib differ from the other tyrosine kinase inhibitors (TKIs) used in the management of gastrointestinal stromal tumours (GIST) (e.g., imatinib, sunitinib, regorafenib) in terms of its mechanism of action and which kinases it inhibits?

Almost all gastrointestinal stromal tumours are driven by activating mutations in KIT (~80%) or the related PDGFRA (~10%) receptor tyrosine kinases.(1,2)

Mutations in the KIT gene at presentation are usually found in exon 9 or 11 in GIST patients. Primary mutations in exon 9 increase receptor dimerization, and those in exon 11 disrupt the auto-inhibited form of the kinase. Both mechanisms cause ligand-independent receptor activation, which leads to uncontrolled cell growth and transformation.(3)

Treatment with TKIs often leads to secondary resistance mutations in KIT in the catalytic domain of the kinase. These mutations frequently map to the embedded conformational switch control mechanism that regulates KIT activity. Secondary

mutations in KIT typically occur in exons 13 and 14 (near the adenosine triphosphate (ATP)-binding pocket) that sterically disrupt drug binding or conformationally activate KIT, and in the activation loop (conformation-controlling switch) encoded by exons 17 and 18.(4,5) Activation loop mutations act by shifting the kinase into an activated conformation that is less amenable to drug binding by any of the currently approved therapies.(6)

First-generation kinase inhibitors in GIST, such as imatinib, sunitinib, and regorafenib, bind to the inactive conformation of the kinase via the adenosine triphosphate binding site. As secondary resistance mutations develop, these TKIs lose their ability to prevent kinase activation, reducing efficacy and leading to cell proliferation. Ripretinib is the first and only switch control kinase inhibitor designed to broadly inhibit wild type and mutated KIT and PDFGRA mutated kinases, including the multiple primary and secondary mutations known to drive disease progression and drug resistance in GIST. Ripretinib's dual mechanism of action precisely and durably binds both the switch pocket region and the activation loop, securing the target kinase into an inactive conformation, preventing downstream signalling and cell proliferation.(7)

In a direct comparison of kinase inhibitors with activity against KIT and/or PDGFRA, ripretinib inhibited cell activity, including kinase phosphorylation and cell proliferation, across various combinations of mutations. Imatinib, sunitinib, and regorafenib exhibited activity against just 7–56% of mutational conditions.(3)

Additionally, ripretinib effectively inhibited all imatinib- and sunitinib-resistant KIT mutants tested and was 3- to >50-fold more potent than regorafenib at inhibiting 18 of 37 tested KIT mutants. Ripretinib was more than 2-fold more potent than regorafenib in 21 of 26 cell lines expressing KIT exon 17/18 switch-activating mutations and was 10- to 20-fold more potent than regorafenib versus the KIT D816V mutation.

Target population and comparators

A2. CS, Section B.3.3, page 89. The CS states *"Whilst patients in the ripretinib arm were offered the option to continue ripretinib treatment following progression in the open-label phase, the continued treatment effect beyond progression is unclear. Therefore, the base-case assumes that patients did not*

continue ripretinib treatment following progression in the open-label phase."

(a) Please clarify if the company is seeking a positive NICE recommendation for the use of ripretinib only up to the point of disease progression, or whether a positive recommendation is also being sought for the continued use of ripretinib beyond progression in patients who are still deriving benefit from it.

(b) Please clarify if clinical opinion was sought regarding whether clinicians would wish to continue ripretinib beyond progression.

a) The company are seeking reimbursement for the use of ripretinib only up to the point of disease progression.

b) UK clinical opinion has been sought as to whether the use of ripretinib would be continued following progression. The clinician advised treatment would generally be stopped at clear/aggressive progression. However, for heavily pre-treated GIST patients, an exception may be made if radiological progression is limited, and the patient is tolerating the therapy. In such cases, treatment would continue while the patient continues to have clinical benefit. This is expected to be the case for a minority of GIST patients and would only occur when no alternative treatment option is available. The decision to continue a patient's current treatment would be made on the basis of scans taken at regular intervals. The frequency of these scans would depend on the hospital, but re-staging would be performed approximately every 2-3 months. If a patient is symptomatic, an earlier scan would be considered.

Limited radiological progression is defined by the UK clinician as only a limited increase in tumour size on radiology, slow radiological increase, and/or no extensive change in the size of the tumour, as well as clinical symptoms remaining manageable and/or have not increased significantly due to the limited progression.

The UK clinician stated that clinical benefit could be due to disease control, clinical symptom control, and/or benefit or maintenance of the patients' quality of life with respect to aspects which are impacted by the disease.

A3. CS, Section B.1.3.3, page 19. The EAG has received clinical advice suggesting that in usual practice: (a) some patients continue to receive

regorafenib after disease progression and (b) if ripretinib was recommended, it may be used beyond disease progression. Please comment on the extent to which the INVICTUS trial represents clinical practice in England.

A UK clinician has stated that they believe the INVICTUS trial to be representative of clinical practice in England. UK patients were recruited into both INVICTUS (n=10, 8%) and the Phase 1 study for ripretinib. As such, UK patients are represented in the clinical trial. The Royal Marsden Hospital in London, UK took part in the Compassionate Use Programme (CUP) and treated 57 patients with ripretinib. In the opinion of the lead physician at the Royal Marsden, the clinical experience and clinical benefit for these patients was very comparable his personal experience of treating patients in the clinical trials and to overall ripretinib clinical trial results.

The clinician advised 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. The principles stated in response to question A2.b. would be followed when deciding to change a patient's treatment, with regard to monitoring tolerability.

Finally, as stated in response to question A2.b. the UK clinician advised 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.

Clinical effectiveness and safety evidence

A4. CS, Section B.2.3, page 29. What was the rationale for patients in the ripretinib group of INVICTUS being permitted to double their dose on progression?

[Response to be provided on Friday 1st July]

A5. CS, Section B.2.3, page 31. Please state the number (and percentage) of patients in the ripretinib arm of INVICTUS who continued to receive ripretinib

after disease progression at: (a) their current dose or (b) an increased dose. Please also provide information on the duration of post-progression ripretinib treatment at each dose (mean, standard deviation and range).

[Response to be provided on Friday 1st July]

A6. CS, Section B.2.3, page 31, Table 8. Patients randomised to the ripretinib group had a lower mean age compared with those in the placebo group. Please comment on the extent to which this might have affected the outcomes observed in the trial.

The HRs shown at the top of the Forest plots in Figure 1 represent the relative influence of treatment effectiveness based on patients' age. The HR values are similar for ages 18-64 years (HR [CI]: [redacted]; 67.1% of the ripretinib population at informed consent, 50% of placebo population at informed consent) and ages 65-74 years (HR [CI]: [redacted]; 23.5% of the ripretinib population at informed consent, 27.3% of placebo population at informed consent).

Figure 1: Forest plot of Progression-free Survival based on Independent Radiologic Review in Double-Blind period in Patient Subgroups (ITT population)

Abbreviations: CI – confidence interval; DCC-2618 – ripretinib; ECOG – Eastern Cooperative Oncology Group; ITT – intention-to-treat.
Data cut-off date: 31st May 2019
Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7)

Additionally, as seen the Forest plot in Figure 2, the objective response rate (ORR) was comparable between all age subgroups. The ripretinib arm shows comparable benefit across subgroups (difference is >0) in all assessed patient subgroups, compared to no effect seen for all patients on placebo.

Figure 2: Forest Plot of Objective Response Rate Based (ORR) on IRR in Patient Subgroups (ITT Population)

Abbreviations: CI – confidence interval; DCC-2618 – ripretinib; ECOG – Eastern Cooperative Oncology Group; IRR – independent radiological review; ITT – intention-to-treat; QD – once daily.
Data cut-off date: 31st May 2019
Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7)

Additionally, it can be seen from the HRs in the subgroup analysis of age groups in INVICTUS in

Table ***1***, based on the latest 15th January 2021 datacut, that the HR for ripretinib vs. placebo (OS) is comparable between each age subgroup.

Table 1: Subgroup analysis of age groups: Ripretinib vs placebo HR

Subgroup	**Ripretinib vs Placebo HR (95% CI)**
18 - 64 Years	[redacted]
>= 65 - 74 Years	[redacted]
75 Years or Older	[redacted]

Abbreviations: CI – confidence interval; HR – hazard ratio.

A7. CS, Section B.2.3, page 31, Table 8. The company's intended positioning for ripretinib is as fourth-line therapy. In INVICTUS, more than one-third of patients had received more than 3 prior therapies. Please comment on the extent to which the number of prior therapies might be prognostic of outcomes.

The HRs shown in Figure 1 represent the relative influence of treatment effectiveness based on receiving 3 or ≥4 lines of prior systemic anti-cancer therapy. The HR values for PFS are similar for 3 prior lines of therapy (HR [CI]: [redacted]) compared with ≥4 prior lines of therapy (HR [CI]: [redacted]), and confidence intervals overlap. This confirms that there is no significant difference in treatment effect for patients who have received 3 vs ≥4 prior lines of therapy, and it is unlikely that number of prior therapies is prognostic of outcomes. Additionally, as seen the Forest plot in Figure 2, the ORR was comparable between patients with 3 prior lines of therapy and patients with ≥4 prior lines of therapy. The ripretinib arm shows comparable benefit in both subgroups, compared to no effect seen for all patients on placebo.

UK clinical opinion was sought regarding the extent to which the number of prior therapies might be prognostic of outcomes in GIST. The clinician stated that the benefit of ripretinib compared to placebo seen in INVICTUS was seen in fourth line patients as well as later line patients. The majority of patients in INVICTUS were fourth line, meaning they had received three prior lines of treatment prior to the study (62.0% of total study population),(7) hence leading the clinician to believe that ripretinib is the best option for both fourth line patients and later lines, where no other treatment options are available.

Additionally, the HR in the OS subgroup analysis of number of prior therapies in INVICTUS in Table 2, based on the latest 15th January 2021 datacut, shows that in subgroup which aligns with the decision problem (patients with 3 prior lines of therapy) there is a strong treatment effect for ripretinib compared with placebo.

Table 2: Subgroup analysis of number of prior therapies: Ripretinib vs placebo HR

Subgroup	Ripretinib vs Placebo HR (95% CI)
3 prior therapies (n=54)	[redacted]
>= 4 prior therapies (n=31)	[redacted]

Abbreviations: CI – confidence interval; HR – hazard ratio.

A8. CS, Section B.2.3, page 31. The NICE final scope states *"If the evidence allows, the following subgroups will be considered: previous treatment with tyrosine kinase inhibitors whose disease has progressed; and resistance or intolerance to tyrosine kinase inhibitors".*

(a) Please state what percentage of patients in INVICTUS (in each trial arm) i) had progressed on prior TKIs, ii) were resistant to TKIs, or iii) were intolerant to TKIs.

(b) Please present forest plots and hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS), sub-grouped into patients who i) had progressed on prior TKIs, ii) were resistant to TKIs, or iii) were intolerant to TKIs.

The inclusion criteria for INVICTUS stated that a patient must have had progressive disease on imatinib, sunitinib, and regorafenib, or had documented intolerance to any of these treatments despite dose modifications.(3) As such, 100% of patients in the INVICTUS trial had progressed on prior TKIs or had documented intolerance to either imatinib, sunitinib, or regorafenib. This is standard inclusion criteria for TKI clinical trials.(8,9) The trial inclusion criteria covers all situations in which treatment can no longer be used or delivers no clinical benefit. The percentage of patients that were resistant or intolerant to TKIs in each trial arm was not recorded, as such these subgroup analyses cannot be performed.

Patients that are resistant to TKIs and patients who have progressed on TKIs are not mutually exclusive or clear in definition, and have substantial overlap, as progression

of KIT-driven tumours is primarily based on development of further KIT resistance mutations.(3) As such, subgroup analysis of patients who were resistant to TKIs is not available, as it would not be possible to differentiate between the three subgroups listed.

A9. CS, Section B.2.6, page 42. Please present Figure 9 of the CS with an additional series showing OS in placebo patients who did not switch to ripretinib, for the extended data cut-off of 15th January 2021.

[Response to be provided on Friday 1st July]

A10. CS, Section B.2.10, page 52 and Section B.3.5, page 94. The incidence of Grade 3/4 anaemia in the ripretinib group is stated as 8/85 (9.4%) in CS Table 16 and as 9/85 (10.6%) in CS Table 29. Please clarify which are the correct data.

The 8/85 (9.4%) incidence of anaemia refers to the primary cut-off date of 31st May 2019,(10) whereas the 9/85 (10.6%) incidence refers to data the long-term update from the 15th January 2021 data cut, 19 months after the primary analysis.(11) The incidence used in the model is 10.6% from the latest (15th January 2021) long-term data update.

A11. CS, Section B.2.10, page 50. Please provide a version of CS Table 15 which includes any drug-related TEAE, any Grade 3/4 drug-related TEAE, and any drug-related treatment-emergent SAE (as in CSR, Table 31).

The safety profile of ripretinib is acceptable relative to the clinical benefit in the context of the treatment of this life-threatening disease. AEs observed with ripretinib are manageable and the drug appears tolerable (7). The incidence of drug-related TEAEs requested is presented in Table 3.

Table 3: Summary of TEAEs in the double-blind phase (safety population)

Categories	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any drug-related TEAE	72 (84.7)	26 (60.5)
Any Grade 3/4 drug-related TEAE	21 (24.7)	7 (16.3)
Any drug-related treatment-emergent SAE	8 (9.4)	3 (7.0)

Abbreviations: SAE - Serious adverse event; TEAE - Treatment-emergent adverse event.
* 44 patients randomised to placebo yet one did not receive treatment

Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7)

A12. CS, Section B.2.10, page 52. Please provide the following tables for the double-blind period of INVICTUS:

(a) Grade 3/4 TEAEs occurring in >2 patients

(b) Serious AEs occurring in >2 patients

(c) AEs of special interest

(d) Please comment on the clinical significance of the observed rates of SCC and actinic keratosis in ripretinib-treated patients.

a)

Table 4: Grade 3/4 Treatment-emergent Adverse Events Reported by >2 Patients by Preferred Term in Double-blind Period (Safety Population)

Preferred term	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any Grade 3/4 event	42 (49.4)	19 (44.2)
Anaemia	8 (9.4)	6 (14.0)
Abdominal pain	6 (7.1)	2 (4.7)
Hypertension	6 (7.1)	0
Hypophosphataemia	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7) von Mehren M, Serrano C, Bauer S, Gelderblom H, George S, Heinrich M, et al. INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as ≥ 4th-line therapy in

patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). Annals of Oncology. 2019 Oct;30:v925–6.(10)

b) Table 5: Treatment-emergent Serious Adverse Events > 2 Patients Preferred Term in Double-blind Period (Safety Population)

Preferred term	Ripretinib (n=85), n (%)	Placebo (n=43)*, n (%)
Any treatment emergent SAE	26 (30.6)	19 (44.2)
Abdominal pain	4 (4.7)	2 (4.7)
Anaemia	3 (3.5)	1 (2.3)
Death	3 (3.5)	4 (9.3)

Abbreviations: SAE – serious adverse event.
Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7)

c) **Table 6: Treatment-emergent Adverse Events of Special Interest by System Organ Class, and Preferred Term in Open Label Period (Safety Population)**

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

Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019(7),

d) UK clinical opinion was sought regarding the clinical significance of the observed rates of SCC and actinic keratosis in ripretinib-treated patients. The clinician stated that the rates of actinic keratosis should always monitored closely, but with an active and well tolerated anti-cancer treatment, dealing with G1-2 keratosis is not a major clinical problem. Regarding SCC, the clinician stated that SCC is an important event, and needs to be carefully monitored. However, in this population of advanced metastatic GIST patients, the benefit of the ripretinib treatment on PFS and OS is far greater that the disadvantage of SCC, given the low incidence in these studies.

A dermatopathological review of cutaneous squamous cell carcinoma (cuSCC) events in patients with gastrointestinal stromal tumour treated with ripretinib was presented at the ESMO 23rd World Congress.(12) This review concluded that, based on the samples analysed (n=10), patients who developed cuSCC lesions while on ripretinib therapy 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 low-risk cuSCC lesions in patients treated with ripretinib can generally be managed using local interventions without the need for dosing modifications or interruptions.

Section B: Clarification on cost-effectiveness data

Survival analysis and switching adjustment

B1. CS, Section B.3.3, page 74. The text states that the OS data used in the model relate to a data cut-off of 15th January 2021. Please clarify if the same data cut-off has also been applied to PFS and AEs. Please update the analysis to use the latest data-cut, if available and necessary.

The data cut-off of 15th January 2021 has also been applied to PFS and AEs used in the cost-effectiveness model. This PFS and AE data is the latest data cut-off as presented in von Mehren et al. 2021 (11).

B2. CS, Section B.3.3, pages 80 to 89. For those patients who switched from placebo to ripretinib, please provide information on the mean time to switching after progression.

The mean time to switching after progression for those patients who switched from placebo to ripretinib was [redacted] weeks (equivalent to less than one model cycle [4.01 weeks]).

B3. CS, Section B.3.3, pages 80 to 89. Where available, please provide the decision rules applied in INVICTUS for: (a) treatment switching to ripretinib

following disease progression on placebo, and (b) continued treatment with ripretinib following disease progression.

(a) Patients randomised to placebo who had disease progression by mRECIST based on independent radiologic review (IRR) were given the option to cross over to receive ripretinib 150 mg QD. Once the IRR had confirmed disease progression, the patient's study drug treatment was unblinded as placebo, and either the patient started the crossover procedures, or discontinued if the patient declined to enter the crossover (13).

(b) Patients who were randomized to ripretinib 150 mg QD and had disease progression defined by mRECIST based on IRR could continue ripretinib at an increased dose of 150 mg BID, or continue treatment on study with the same dose if the Investigator felt the patient was receiving benefit from ripretinib or if dose escalation may not be tolerable for the patient, or discontinue ripretinib (13).

B4. CS, Section B.3.3, pages 80 to 89. For the two-stage treatment switching analysis (placebo to ripretinib) please provide more information, including the model(s) considered along with the justification for the base case model (such as clinical plausibility and goodness-of-fit) and time ratio treatment effect associated with continuing ripretinib treatment. If only one model type (such as Weibull, log-normal, log-logistic) has been considered, please include additional scenarios demonstrating the impact of using different model types.

Log-normal, Weibull, log-logistic, exponential and generalised gamma models were considered for the two-stage treatment switching analysis. Log-normal was chosen as the model for the base case since it had the lowest AIC for both placebo and ripretinib (Table 7). This aligned with the base case curve used for OS extrapolation, which was also log-normal.

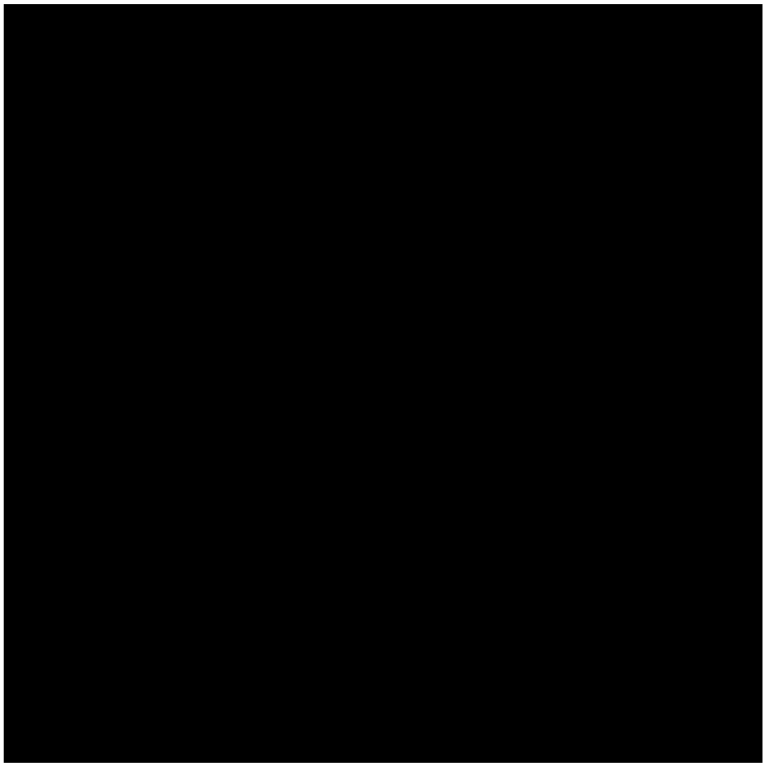
Table 7: AIC values and time ratios for the different AFT models used in the TSE method

	Log-normal	Weibull	Log-logistic	Exponential	Generalised gamma
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike information criterion. **Bold** highlight indicates the lowest AIC value.

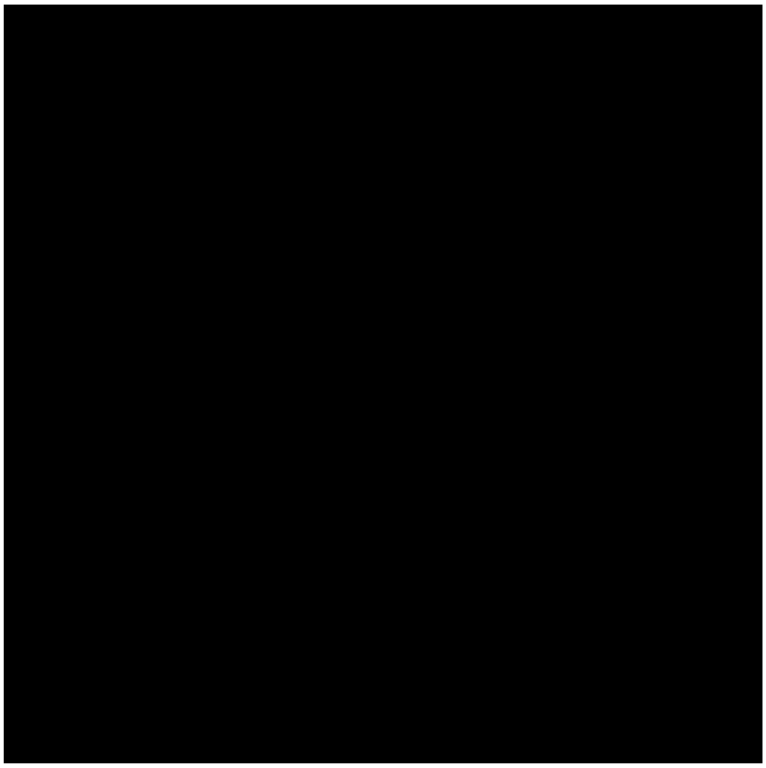
The KM curves for each model can be seen in Figure 3-Figure 7. The median OS for each model can be seen in Table 8.

Figure 3: BSC OS KM curve adjusted using log-normal model



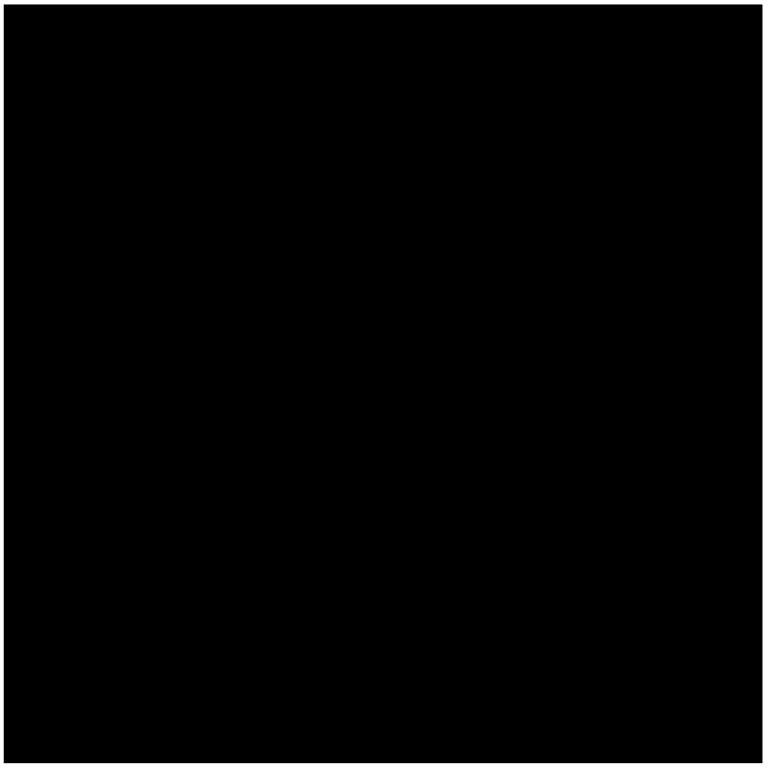
Abbreviations: BSC – Best supportive care.

Figure 4: BSC OS KM curve adjusted using Weibull model



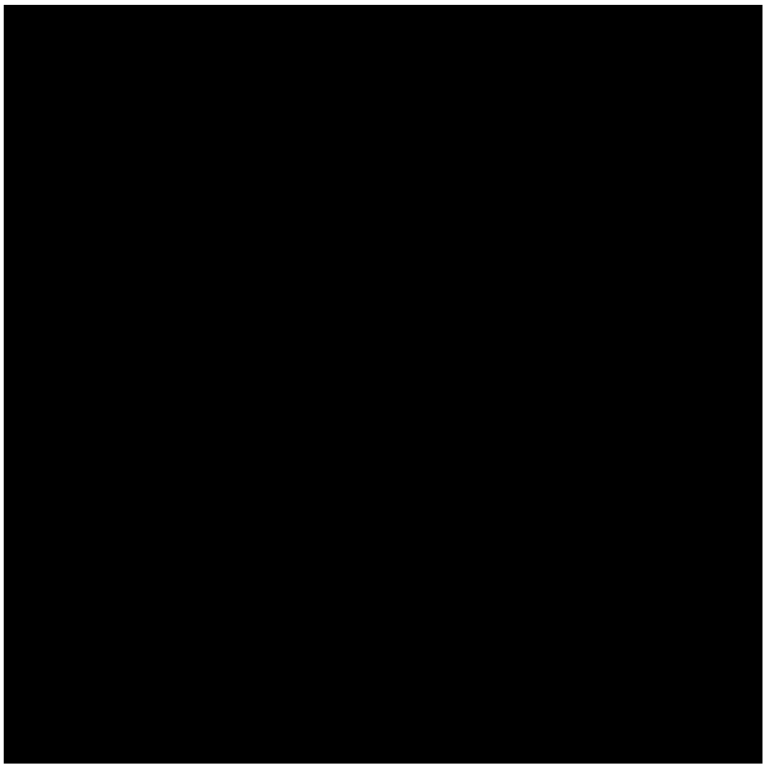
Abbreviations: BSC – Best supportive care.

Figure 5: BSC OS KM curve adjusted using log-logistic model



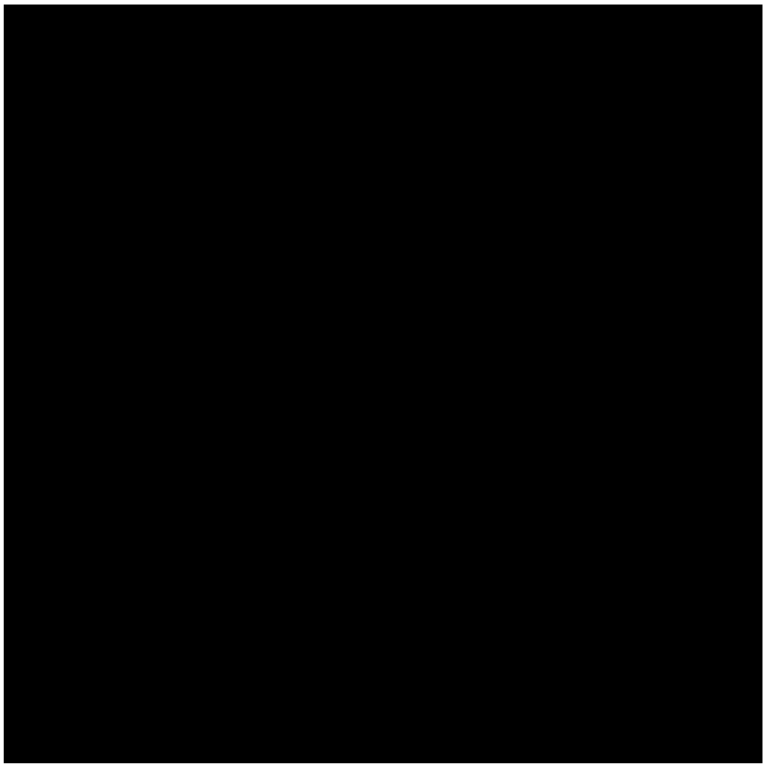
Abbreviations: BSC – Best supportive care.

Figure 6: BSC OS KM curve adjusted using exponential model



Abbreviations: BSC – Best supportive care.

Figure 7: BSC OS KM curve adjusted using generalised gamma model



Abbreviations: BSC – Best supportive care.

Table 8: Median OS BSC times for each model

	Log-normal	Weibull	Log-logistic	Exponential	Generalised gamma
Median OS BSC (weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; OS – Overall survival.

The exponential model is clearly not clinically plausible since it extends OS to [redacted] weeks. All other AFT models were similar in the reported OS and therefore the AIC value was used to select the most appropriate model.

B5. CS, Section B.3.8, Table 45, page 116. Please provide more information on the ripretinib post-progression adjustment (*"simple two-stage with re-censoring"*) which is presented in the economic scenario analyses. This should include the information already provided in the CS for the placebo to ripretinib switching analysis, as well as the additional information requested in question B4.

As per the study design for INVICTUS, study drug treatment was unblinded upon disease progression and patients randomised to ripretinib were given the option to continue to receive open-label ripretinib. Whilst ripretinib is not expected to be reimbursed beyond progression in the UK, it is unclear whether continued treatment beyond progression with ripretinib confers any benefit. As such, ITT data was used directly to model OS for ripretinib patients, with a scenario analysis conducted to account for continuation beyond progression by adjusting the ripretinib OS using the two-stage method.

The two-stage approach relies on the following assumptions (14):

- A secondary baseline can be defined, at which point patients are at risk of crossover (for example progression).
- No unmeasured confounding at the point of the secondary baseline.
- The RCT (INVICTUS) is appropriately randomised up until the point of disease progression.

Two models were explored, one of which included time to progression as a co-variate (simple model) and another which included the time to progression, Eastern Cooperative Oncology Group performance status (ECOG), quality of life (QoL) and age as co-variates. The following assumption was made: ECOG PS and QoL at progression values recorded at the closest time point to progression were used in the analysis.

As time to progression was the only statistically significant co-variate and the use of co-variates in the complex model would add additional uncertainty to the analysis, given the small sample size, the simple model was employed in the base-case analysis.

The resulting time ratio was then used to 'shrink' the post-progression survival times of patients who continued ripretinib treatment to derive a counterfactual dataset unaffected by continuation. Censored progression time was assumed to be equal to documented progression time. The base-case analysis was performed with recensoring to guard against informative censoring (15). Informative censoring occurs when participants are lost to follow-up due to reasons related to the study and can result in biased estimates of treatment effect if not accounted for (15,16). The resulting median OS times for the base-case analysis (simple model) and complex model are presented in Table 9. The unadjusted and adjusted OS ripretinib base-case KM curves are shown in Figure 8- Figure 10.

The two-stage adjustment simple model led to a shorter OS compared to the two-stage adjustment complex model. Therefore, use of the simple model in the base-case analysis is a conservative approach.

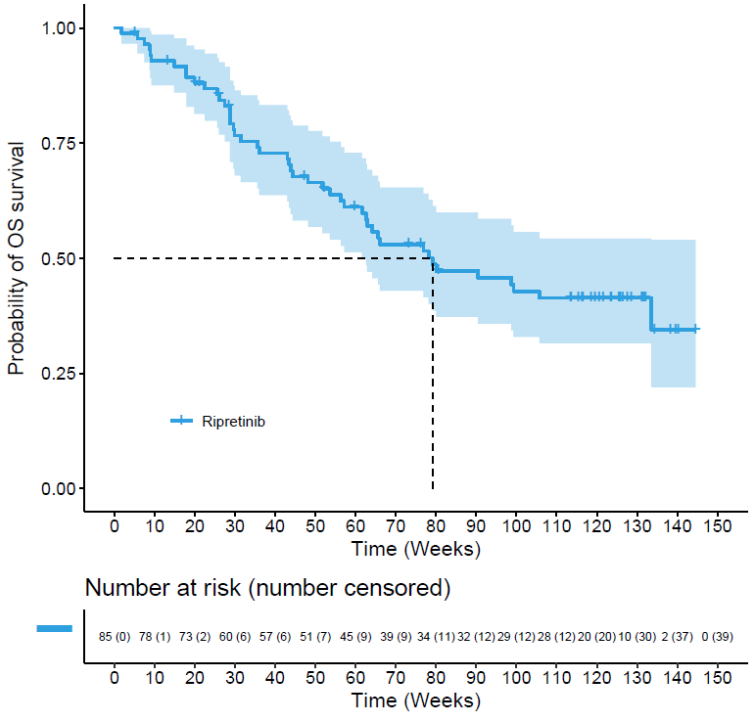
Table 9: Median OS times ripretinib

Crossover adjustment method	**Median OS ripretinib (weeks)**
Unadjusted	79.14
Two-stage adjustment simple model (treatment switch, time to progression as co-variates)	[redacted]

Two-stage adjustment complex model (treatment switch, time to progression, ECOG PS, age and QoL)	[redacted]

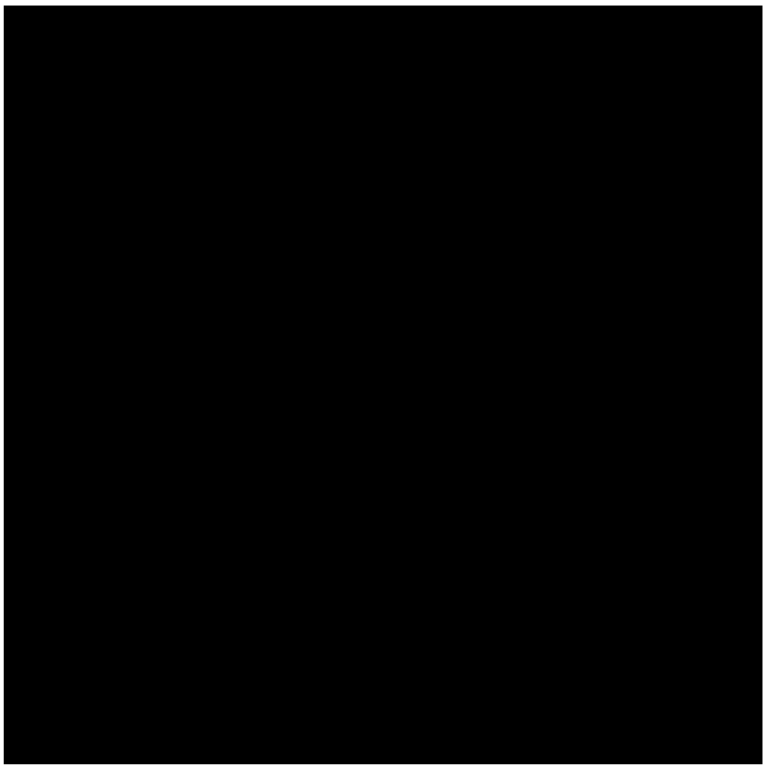
Abbreviations: BSC - Best supportive care; ECOG PS – Eastern Cooperative Oncology Group performance status; OS – Overall survival; QoL – quality of life.

Figure 8: KM curve unadjusted OS ripretinib



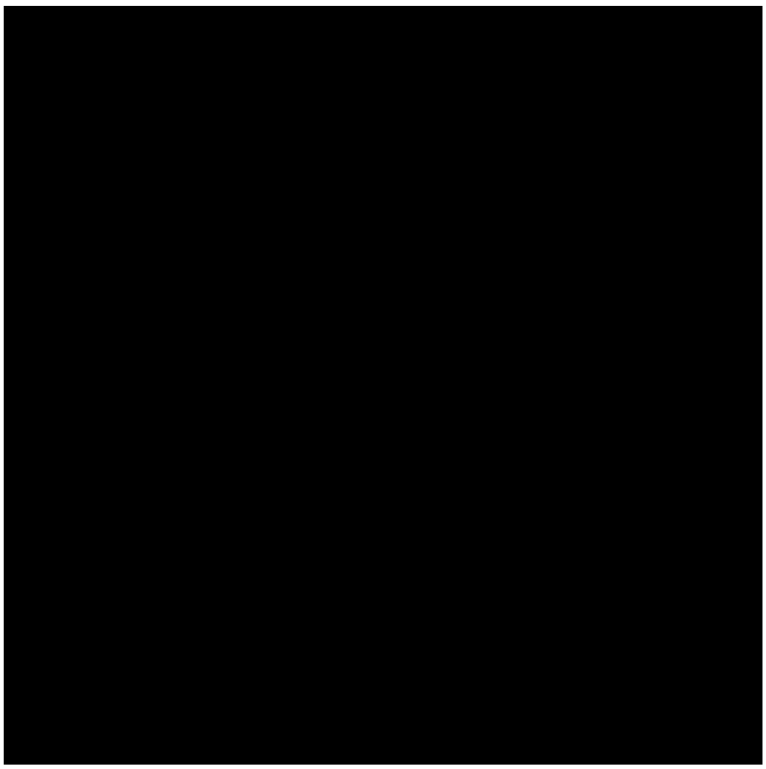
Abbreviations: ITT – Intention-to-treat; OS – Overall survival.

Figure 9: KM curve adjusted OS ripretinib – two-stage adjustment simple model



Abbreviations: ITT – Intention-to-treat; OS – Overall survival.

Figure 10: KM curve adjusted OS ripretinib – two-stage adjustment complex model



Abbreviations: ITT – Intention-to-treat; OS – Overall survival.

For the two-stage treatment switching analysis, Weibull, log-normal, log-logistic, exponential, and generalised gamma models were considered. Log-normal was chosen as the model for the base case since it had the lowest AIC value (Table 10). This aligned with the base case curve used for OS extrapolation, which was also log-normal.

Table 10: AIC values and time ratios for the different AFT models used in the TSE method

	Log-normal	Weibull	Log-logistic	Exponential	Generalised gamma
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike information criterion. **Bold** highlight indicates the lowest AIC value.

The KM curves for each model can be seen in Figure 11 - Figure 14. The median OS for each model can be seen in Table 11.

Figure 11: Ripretinib OS KM curve adjusted using Weibull model

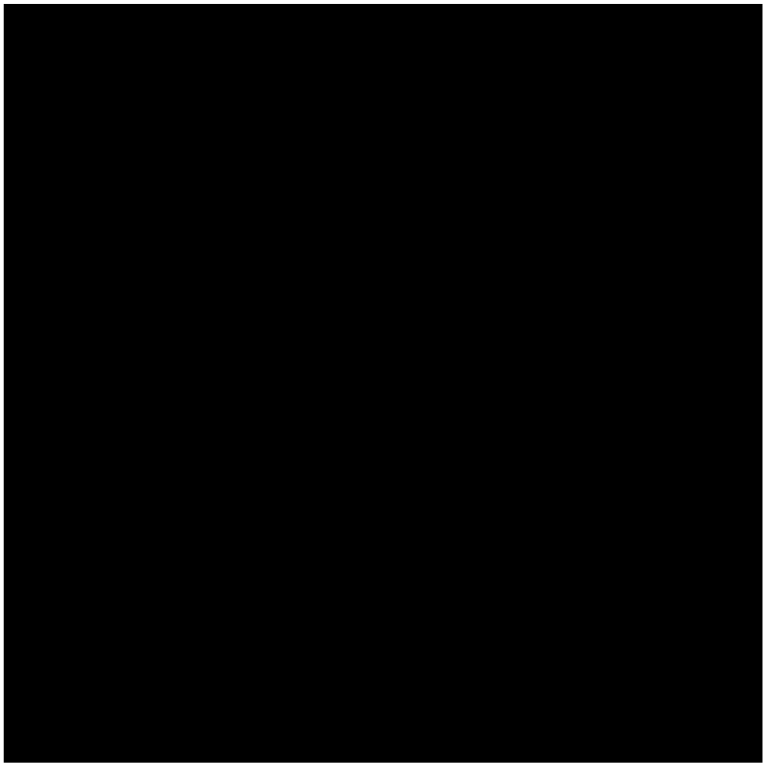


Figure 12: Ripretinib OS KM curve adjusted using log-logistic model

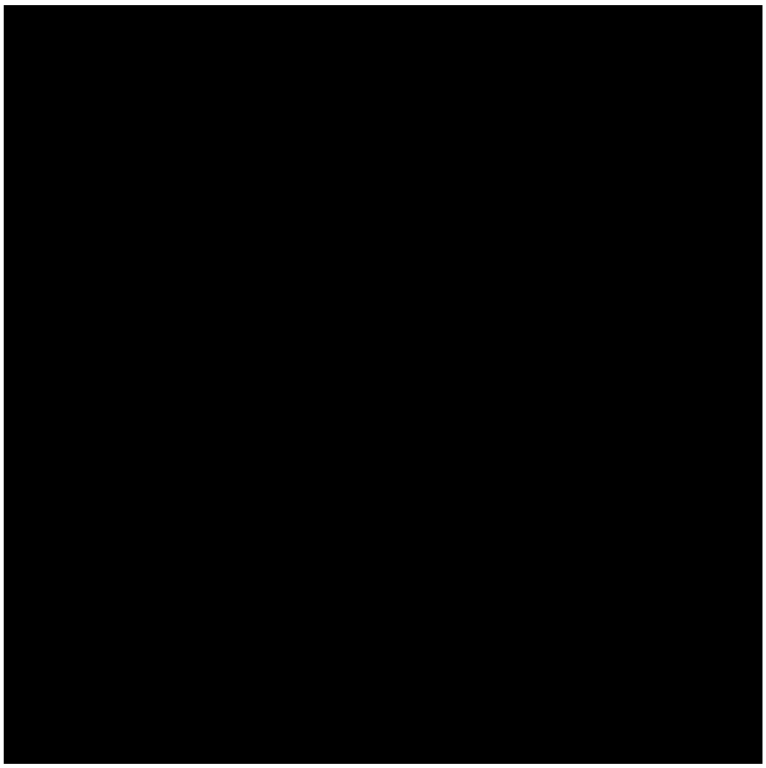


Figure 13: Ripretinib OS KM curve adjusted using exponential model

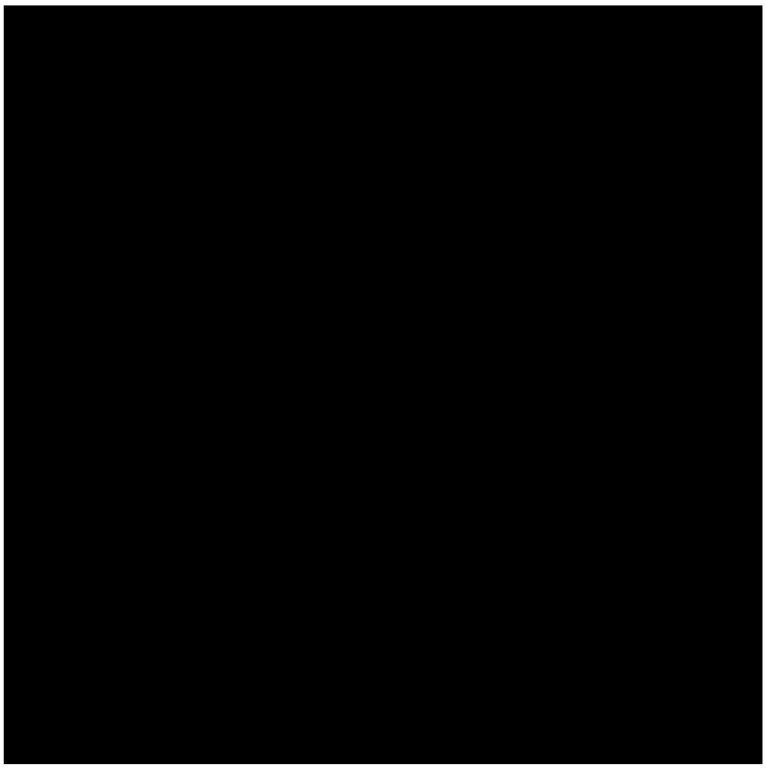


Figure 14: Ripretinib OS KM curve adjusted using generalised gamma model

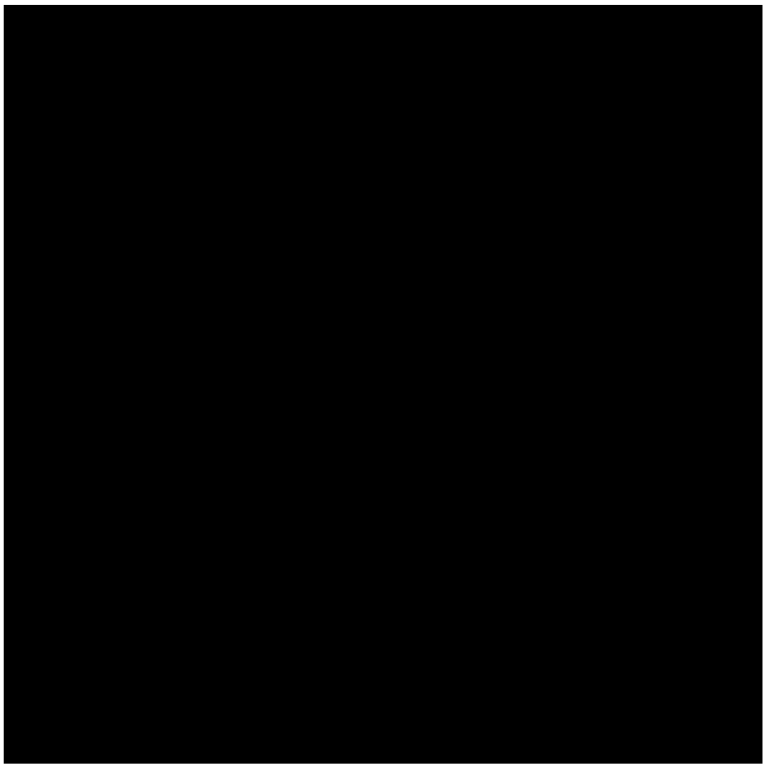


Table 11: Median OS ripretinib times for each model

	Log-normal	Weibull	Log-logistic	Exponential	Generalised gamma
Median OS ripretinib (weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS – Overall survival.

The exponential model is not clinically plausible since it extends OS beyond 100 weeks. All other AFT models were similar in the reported OS and therefore the AIC value was used to select the most appropriate model, the log-normal model. Only using the Weibull or generalised gamma models would have led to a higher OS estimate for ripretinib.

B6. CS, Section B.3.3, page 84. The CS states that *"With respect to the time to progression values, 7 of the 44 patients in the placebo group experienced censored progression but continued to be followed up after this. To avoid reducing an already small sample size, it was assumed that the censored time*

to progression values equated to documented time to progression for these patients." **Please clarify if these seven patients had switched treatment and confirm that this assumption was only used for the treatment switching analysis.**

Of the 7 patients in the placebo group who experienced censored progression but continued to be followed up afterwards, 3 of these patients crossed over to ripretinib treatment. This assumption was only used for the treatment switching analysis.

B7. CS, Section B.3.3, pages 80 to 89. Please explain how judgements about clinical plausibility were used to inform parametric survival model selection.

To validate the choice of parametric curves, a visual assessment was first carried out to determine whether the independent parametric curves fitted the data and produced good visual predictions for ripretinib and BSC within the observed period. Additionally, the AIC and BIC statistical goodness-of-fit data was assessed to determine the best statistical fit, by choosing the lowest AIC values. A combination of best visual fit and best statistical fit was used to inform the choice of parametric survival model.

To validate the clinical plausibility of the parametric survival models chosen, the median PFS (ripretinib and BSC) and OS (ripretinib) predicted by the model were compared against data in the INVICTUS study (15th January 2021 data cut), as shown in Table 12. Predicted landmark survival rates compared to the INVICTUS trial (15th January 2021 data cut) trial KM curves are presented in Table 13. The comparison demonstrates that the model closely predicts the clinical data for ripretinib and BSC.

Table 12: Summary of model predicted outcomes compared with INVICTUS trial data, ITT population

Outcome	Clinical trial result, median weeks	Model result, median weeks
Ripretinib		
PFS	27.57	[redacted]
OS	79.14	[redacted]
BSC		
PFS	4.14	[redacted]

Abbreviations: BSC – Best supportive care; OS – Overall survival; PFS – Progression-free survival.

Table 13: Summary of model predicted landmark rates compared with clinical data, ITT population

Distribution	Weeks				
	26	**52**	**78**	**104**	**130**
Ripretinib					
PFS KM data	51%	22%	12%	5%	2%
PFS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS KM data	84%	65%	52%	43%	41%
OS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	13	**26**	**39**	**52**	**65**
BSC					
PFS KM data	13%	3%	3%	N/A	N/A
PFS extrapolated data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; KM – Kaplan-Meier; N/A – Not applicable; OS – Overall survival; PFS – Progression-free survival.

B8. CS, Section B.3.3, pages 74 to 89. The model assumes a lifetime treatment effect. Please provide an analysis of the HRs for OS of ripretinib versus switching-adjusted BSC over time to explore the plausibility of this assumption. Please also comment on whether clinical opinion has been sought around this assumption. If a positive approval is only being sought for ripretinib up to the point of progression (see question A2(a)), please conduct a similar analysis including switching adjustment in both treatment groups.
[Response to be provided on Friday 1st July]

HRQoL parameters

B9. The model applies utility values for the progression-free and post-progression states of [redacted] and [redacted], respectively, based on EQ-5D-5L assessments in INVICTUS which have been mapped to the EQ-5D-3L.

- **(a) The post-progression utility value is very similar to the progression-free value. Please comment on why this might be the case.**
- **(b) Please comment on whether the EQ-5D-5L data collection mechanism in INVICTUS might be subject to potential informative censoring. On average, how long after progression were the post-progression EQ-5D assessments?**
- **(c) Please provide information on the mean EQ-5D-5L utility value and number of observations for each trial cycle and for the final treatment visit. Please present these data split by treatment group and whether the patients are still on treatment.**
- **(d) Please provide estimates of overall mean EQ-5D for the following states: progression-free (PF) on treatment, PF off treatment, progressed disease (PD) on-treatment, and PD off-treatment.**

[Response to be provided on Friday 1st July]

B10. The model does not include any adjustment of utility values for increasing age. Please clarify why this has not been included in the model. Please update the model to include age-adjusted utility values using a multiplicative approach based on general population EQ-5D estimates reported by Hernandez Alava *et al.* (2022).

[Response to be provided on Friday 1st July]

Cost parameters

B11. CS, Section B.3.5, page 98. The model includes compliance and relative dose intensity (RDI) estimates of [redacted] and [redacted], respectively, based on the double-blind period of INVICTUS.

(a) Please comment on whether applying both of these parameters together will underestimate drug costs (i.e., does RDI not already include compliance?).

(b) Please provide estimates of compliance and RDI for the whole trial period, including post-progression ripretinib use (note – the EAG would suggest that overall RDI should be calculated according to the dosing applied in the double-blind phase, i.e., at a planned dose of 150mg QD).

a) The company thank the ERG for bringing this to our attention. The definition of compliance stated in the CSR for the INVICTUS is: (total number of days dosed/treatment duration in days)*100.(7) The definition of relative dose intensity stated in the CSR for the INVICTUS trial is: (total dose received/total planned dose)*100.(7) As RDI does not exclude days that a patient is not dosed as planned, there is overlap between these calculations. Applying these estimates concurrently together will underestimate drug costs. The model has been corrected to include 100% compliance to overcome this error.

b) As described in response to question A2, the company is only seeking reimbursement up to progression, therefore post-progression use of ripretinib is irrelevant for the decision problem The calculations for compliance and RDI over the whole trial period (calculated according to the dosing applied in the double-blind phase) are shown in Table 14.

Table 14: RDI and compliance calculations for whole trial period.

Parameter	Ripretinib (QD)			Ripretinib (BID)*	Derived weighted average**
	Double-blind	Open label	Open label (crossover from placebo)	Open label	
n	[redacted]	[redacted]	[redacted]	[redacted]	
Treatment duration (years)	[redacted]	[redacted]	[redacted]	[redacted]	
Patient years	[redacted]	[redacted]	[redacted]	[redacted]	
Compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*RDI has been calculated according to the dosing applied in the double-blind phase.
**The derived weighted average is calculated by weighting the compliance and RDI, respectively, by the number of patient years (treatment duration*number of patients) in the respective phases of the trial.
Abbreviations: BID – twice daily; n – number; QD – once daily; RDI – relative dose intensity.
Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7)

B12. CS, Section B.3.5, page 97. Drug acquisition costs are calculated as a function of half-cycle corrected PFS, the cost of ripretinib per day, the number of days per cycle, compliance and RDI. This approach ignores drug wastage. Please comment on whether this omission was intentional. If this was not intentional, please amend the model.

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.

B13. CS Section B.1.2, Table 2, page 13. Table 2 states that additional monitoring is required for patients with a history of high blood pressure or heart conditions. Please comment on whether these additional costs are captured in the modelled costs. Please amend the model to include these additional costs, if necessary.

The resource use and monitoring costs applied in the model are comparable to those applied in the NICE STA of regorafenib (TA488). Resource use frequency for TA488 was derived through a resource use survey conducted in 2013 and involving 15 physicians from England and Wales. They reported that full blood count and liver function tests as well as CT and MRI scans are usually carried out for GIST patients. The findings from that survey were revalidated in 2016 by two consultant oncologists based on clinical practice in England. Based on the evidence collected through the two physician surveys, it was determined that no further tests or monitoring visits were required for the administration of regorafenib.(17) The SmPC for regorafenib states that patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms, and that blood pressure should be monitored, and hypertension treated in accordance with standard medical practice.(18) This is comparable in terms of resource use to SmPC for ripretinib, which states that blood pressure should be monitored as clinically indicated, and that ejection fraction should be monitored in patients with cardiac failure.(19) Additionally, ejection fraction can be measured through echocardiogram (ECG), which should be monitored in patients with cardiac failure regardless of treatment with ripretinib,(20,21) or through MRI or CT scan, which are included in the resource use and monitoring costs in the model.(20) As such, monitoring costs associated with the use of ripretinib are already incorporated into the CEM.

Executable model

B14. The EAG has identified several apparent minor programming errors in the company's executable model. Please investigate each of the following issues, confirm if each is an error and provide an updated version of the executable model including all necessary corrections.

(a) Model, worksheet "Data Store", cells D120:E220. The model uses life tables for the UK rather than England. Life tables for England should be used.

(b) Model, worksheet "Data Store", cells F120:F220. The general population mortality risk calculations assume that men and women have different risks of death at each age x, whilst also assuming that the same proportion of men and women will apply in each model cycle. Both assumptions cannot simultaneously be true. The EAG believes it would be more appropriate to use a weighted survival model (i.e., generate general population survival models for men and women and weight them by the proportion of men/women only at baseline).

(c) Model, worksheet "Data Store" cells K222:K1535. These calculations calculate the risk of general population death in each model cycle. However, the lookup function is referring to values for age x+1 year rather than age x. For example, the calculation in cell H180 shows that the estimated risk of death for an individual who has survived up to age 60 is 0.00052125. However, the first 13 model cycles use an estimate of 0.000566, which is the risk for an individual who has already survived up to age 61.

(d) Model, worksheet "Clinical Inputs" cells I69:I589 and L69:L589. These formulae apply a constraint which determines whether the risk of death with the disease is greater than or equal to the risk of death in the general population. If the condition is met, the value returned is the cumulative survival probability from the unadjusted OS survival function. The EAG 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).

(e) Model, worksheet "Clinical Inputs", cells E69:F589. No constraint has been applied to the PFS function. At a minimum, a logical consistency constraint should be applied to ensure that the cumulative PFS probability can never be higher than the cumulative OS probability.

(f) Model, worksheets "Trace (Ripretinib)" and "Trace (BSC)", all subsequent calculations dependent on cells I9:K10. The half-cycle correction has been applied inappropriately as the first interval is counted 1.5 times.

(g) Model, worksheets "Trace (Ripretinib)" and "Trace (BSC)", cells C9:C22. The year is rounded down to the nearest integer value in all cycles in the first year, but is not rounded down in any subsequent cycles. This will impact on discounting. The EAG would prefer not to round down the discounting multipliers, but even if this approach is preferred by the company, it should be consistent across all model cycles.

(h) Model, worksheet "Results", cell E10:E11. Life years gained (LYGs) have been discounted. The EAG believes that it is more informative to report undiscounted LYGs as these are the values which will inform discussions around the End of Life (EoL) criteria.

(i) Model, worksheets "Trace (Ripretinib)" and "Trace (BSC)", column C. Each cycle is assumed to be 1/13 years in duration. The calculations in this column assume that there are 52 weeks in a year. However, there are approximately 52.17 weeks in a year. The model should consistently deal with time units throughout.

(j) Model, worksheet "Survival analysis" cells D61:AP593. The survivor functions in this worksheet define the time unit *t* as 1/13th of a year. Please confirm that this same time unit was used in the underlying time-to-event data when fitting parametric survival models (i.e., was each unit of time *t* defined as 28.0962 days? Or was it defined as 28 days, or months?).

(k) Model, worksheets "Trace (Ripretinib)" and "Trace (BSC)", cells S10:S528. The discount rate multiplier is only being applied to the latter part of the cost calculation – extra brackets are needed.

(l) Model, worksheets "Trace (Ripretinib)" and "Trace (BSC)", column AE. The EoL cost has not been discounted in either group.

(m) Model, worksheet "Model Parameters". Independent beta distributions are used to sample health state utilities. As the values for both states are similar, this allows logically inconsistent samples whereby the utility value for PF is higher than that for PD in some samples. It would be more appropriate to apply a disutility approach which can handle ordered data, e.g., the approach described by Ren *et al.*, *PharmacoEconomics*, 2018, vol. 36).

[Response to be provided on Friday 1st July]

Section C: Additional analysis requests

C1. Please provide a Kaplan-Meier plot of time to treatment discontinuation in the ripretinib arm of INVICTUS (including those who continued ripretinib treatment beyond progression), including numbers of patients at risk. Please fit parametric survival models to the available time-to-event data and select a preferred model using the approach described in Decision Support Unit Technical Support Document 14.

[Response to be provided on Friday 1st July]

C2. Please provide Kaplan-Meier plots of post-discontinuation survival in the ripretinib group. Please provide Kaplan-Meier plots of post-progression survival in both groups (unadjusted for switching).

[Response to be provided on Friday 1st July]

C3. For PFS and OS, please provide plots of the empirical/unsmoothed and smoothed hazard function for the data used in the analysis. Please also plot the hazard function of each of the parametric survival models on top of the empirical and smoothed hazard.

[Response to be provided on Friday 1st July]

C4 If it is the company's intention is to seek a positive NICE recommendation only in patients who have not yet progressed on ripretinib, please provide an extended switching analysis which adjusts for potential confounding associated with the continued use of post-progression ripretinib in the

INVICTUS trial. If this is what has already been done in the scenario analysis labelled "Simple two-stage with recensoring" in CS Table 45, this question can be ignored.

As described in response to question A2, the company is only seeking reimbursement up to progression. In the scenario analysis labelled "Simple two-stage with recensoring", the company has adjusted for use of post-progression ripretinib in the INVICTUS trial.

C5. The EAG has received clinical advice suggesting that patients who have failed three prior therapies might continue to receive regorafenib beyond disease progression. Please provide an exploratory economic analysis comparing ripretinib versus continued regorafenib at fourth-line.

Regorafenib is not considered a relevant comparator in the fourth-line. This is aligned with the final NICE scope which lists the comparators of ripretinib as established clinical management without ripretinib including best supportive care. This also aligns to input from a UK clinician that for third-line GIST patients treated with regorafenib, even after the introduction of ripretinib, treatment with regorafenib would not be affected, i.e., patients would continue regorafenib treatment if the patient is still doing well in the clinician's opinion and is still receiving clinical benefit. The clinician also stated that no rechallenge occurs in the UK with any TKIs (including imatinib, sunitinib and regorafenib); once a patient has failed a therapy, they do not repeat it.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

6th June 2022

File name	Version	Contains confidential information	Date
ID3805 ripretinib clarification letter to company [AIC]	**2.0**	**Yes**	**01/07/22**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Mechanism of action

A1. Company submission (CS), Section B.1.2, page 12. How does ripretinib differ from the other tyrosine kinase inhibitors (TKIs) used in the management of gastrointestinal stromal tumours (GIST) (e.g., imatinib, sunitinib, regorafenib) in terms of its mechanism of action and which kinases it inhibits?

[Response already provided on 24th June]

Target population and comparators

A2. CS, Section B.3.3, page 89. The CS states *"Whilst patients in the ripretinib arm were offered the option to continue ripretinib treatment following progression in the open-label phase, the continued treatment effect beyond progression is unclear. Therefore, the base-case assumes that patients did not continue ripretinib treatment following progression in the open-label phase."*

(a) Please clarify if the company is seeking a positive NICE recommendation for the use of ripretinib only up to the point of disease progression, or whether a positive recommendation is also being sought for the continued use of ripretinib beyond progression in patients who are still deriving benefit from it.

(b) Please clarify if clinical opinion was sought regarding whether clinicians would

wish to continue ripretinib beyond progression.
[Response already provided on 24th June]

A3. CS, Section B.1.3.3, page 19. The EAG has received clinical advice suggesting that in usual practice: (a) some patients continue to receive regorafenib after disease progression and (b) if ripretinib was recommended, it may be used beyond disease progression. Please comment on the extent to which the INVICTUS trial represents clinical practice in England.
[Response already provided on 24th June]

Clinical effectiveness and safety evidence

A4. CS, Section B.2.3, page 29. What was the rationale for patients in the ripretinib group of INVICTUS being permitted to double their dose on progression?

The rationale for permitting patients in the ripretinib group of INVICTUS to double their dose on progression was based on clinical data from the phase 1 study (NCT02571036). In the dose-escalation phase of this study, the doses tested included 20 mg (n=4), 30 mg (n=4), 50 mg (n=11), 100 mg (n=12), 150 mg (n=6), and 200 mg (n=7) twice a day (BID) and 100 mg (n=6), 150 mg (n=12), and 250 mg (n=6) once daily (QD). The maximum tolerated dose was not reached among the doses tested, including ripretinib 200 mg twice daily (1).

Based on the safety, pharmacokinetic, and pharmacodynamic results of the phase 1 study, ripretinib 150 mg QD was established as the recommended phase 2 dose. Ripretinib 150 mg BID in the dose-escalation phase of the phase 1 study was well-tolerated without significant dose-limiting toxicity in patients with advanced GIST (2).

Given the acceptable safety profile of ripretinib 150 mg BID, patients in the phase 3 INVICTUS study (NCT03353753) were offered the option of ripretinib intra-patient dose escalation to 150 mg BID after disease progression on ripretinib 150 mg QD, given the lack of alternative treatment options (2). The company would like to reiterate that reimbursement of ripretinib is not being sought for BID dosing.

A5. CS, Section B.2.3, page 31. Please state the number (and percentage) of patients in the ripretinib arm of INVICTUS who continued to receive ripretinib after disease progression at: (a) their current dose or (b) an increased dose. Please also provide information on the duration of post-progression ripretinib treatment at each dose (mean, standard deviation and range).

As of Aug 10, 2020, 65 patients randomized to ripretinib 150 mg QD had PD by BICR. Of these, 43 patients received ripretinib IPDE to 150 mg b.i.d., and 22 patients either continued ripretinib 150 mg QD or discontinued study treatment. The median duration of treatment with ripretinib 150 mg b.i.d. was 3.7 months (range, 1 day–18.6 months), and 26% (11 of 43 patients) received ripretinib 150 mg b.i.d. for 6 months or longer (3).

As described in response to question A2, the company is only seeking reimbursement up to progression, therefore post-progression use of ripretinib is irrelevant for the decision problem. An analysis regarding duration (mean, standard deviation and range) of post-progression ripretinib treatment at each dose has not been performed for the latest data cut and incorporating post-progression ripretinib treatment would lead to bias the assessment against ripretinib.

A6. CS, Section B.2.3, page 31, Table 8. Patients randomised to the ripretinib group had a lower mean age compared with those in the placebo group. Please comment on the extent to which this might have affected the outcomes observed in the trial.
[Response already provided on 24th June]

A7. CS, Section B.2.3, page 31, Table 8. The company's intended positioning for ripretinib is as fourth-line therapy. In INVICTUS, more than one-third of patients had received more than 3 prior therapies. Please comment on the extent to which the number of prior therapies might be prognostic of outcomes.
[Response already provided on 24th June]

A8. CS, Section B.2.3, page 31. The NICE final scope states *"If the evidence allows, the following subgroups will be considered: previous treatment with tyrosine kinase inhibitors whose disease has progressed; and resistance or intolerance to tyrosine*

kinase inhibitors".

(a) Please state what percentage of patients in INVICTUS (in each trial arm) i) had progressed on prior TKIs, ii) were resistant to TKIs, or iii) were intolerant to TKIs.

(b) Please present forest plots and hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS), subgrouped into patients who i) had progressed on prior TKIs, ii) were resistant to TKIs, or iii) were intolerant to TKIs.

[Response already provided on 24th June]

A9. CS, Section B.2.6, page 42. Please present Figure 9 of the CS with an additional series showing OS in placebo patients who did not switch to ripretinib, for the extended data cut-off of 15th January 2021.

Figure 1 presents median OS from the extended data cut-off of 15th January 2021. In placebo patients who did not switch to ripretinib, median OS was [redacted].

Figure 1: Mature OS from extended follow-up (data cut-off 15th January 2021, including placebo patients who did not switch to ripretinib

Abbreviations: CI – Confidence interval; OS – Overall survival.

A10. CS, Section B.2.10, page 52 and Section B.3.5, page 94. The incidence of Grade 3/4 anaemia in the ripretinib group is stated as 8/85 (9.4%) in CS Table 16 and as 9/85 (10.6%) in CS Table 29. Please clarify which are the correct data.
[Response already provided on 24th June]

A11. CS, Section B.2.10, page 50. Please provide a version of CS Table 15 which includes any drug-related TEAE, any Grade 3/4 drug-related TEAE, and any drug-related treatment-emergent SAE (as in CSR, Table 31).

[Response already provided on 24th June]

A12. CS, Section B.2.10, page 52. Please provide the following tables for the double-blind period of INVICTUS:

(a) Grade 3/4 TEAEs occurring in >2 patients
(b) Serious AEs occurring in >2 patients
(c) AEs of special interest
(d) Please comment on the clinical significance of the observed rates of SCC and actinic keratosis in ripretinib-treated patients.

[Response already provided on 24th June]

Section B: Clarification on cost-effectiveness data

Survival analysis and switching adjustment

B1. CS, Section B.3.3, page 74. The text states that the OS data used in the model relate to a data cut-off of 15th January 2021. Please clarify if the same data cut-off has also been applied to PFS and AEs. Please update the analysis to use the latest data-cut, if available and necessary.

[Response already provided on 24th June]

B2. CS, Section B.3.3, pages 80 to 89. For those patients who switched from placebo to ripretinib, please provide information on the mean time to switching after progression.

[Response already provided on 24th June]

B3. CS, Section B.3.3, pages 80 to 89. Where available, please provide the decision rules applied in INVICTUS for: (a) treatment switching to ripretinib following disease progression on placebo, and (b) continued treatment with ripretinib following disease progression.
[Response already provided on 24th June]

B4. CS, Section B.3.3, pages 80 to 89. For the two-stage treatment switching analysis (placebo to ripretinib) please provide more information, including the model(s) considered along with the justification for the base case model (such as clinical plausibility and goodness-of-fit) and time ratio treatment effect associated with continuing ripretinib treatment. If only one model type (such as Weibull, log-normal, log-logistic) has been considered, please include additional scenarios demonstrating the impact of using different model types.
[Response already provided on 24th June]

B5. CS, Section B.3.8, Table 45, page 116. Please provide more information on the ripretinib post-progression adjustment (*"simple two-stage with re-censoring"*) which is presented in the economic scenario analyses. This should include the information already provided in the CS for the placebo to ripretinib switching analysis, as well as the additional information requested in question B4.
[Response already provided on 24th June]

B6. CS, Section B.3.3, page 84. The CS states that *"With respect to the time to progression values, 7 of the 44 patients in the placebo group experienced censored progression but continued to be followed up after this. To avoid reducing an already small sample size, it was assumed that the censored time to progression values equated to documented time to progression for these patients."* Please clarify if these seven patients had switched treatment and

confirm that this assumption was only used for the treatment switching analysis.

[Response already provided on 24th June]

B7. CS, Section B.3.3, pages 80 to 89. Please explain how judgements about clinical plausibility were used to inform parametric survival model selection.

[Response already provided on 24th June]

B8. CS, Section B.3.3, pages 74 to 89. The model assumes a lifetime treatment effect. Please provide an analysis of the HRs for OS of ripretinib versus switching-adjusted BSC over time to explore the plausibility of this assumption. Please also comment on whether clinical opinion has been sought around this assumption. If a positive approval is only being sought for ripretinib up to the point of progression (see question A2(a)), please conduct a similar analysis including switching adjustment in both treatment groups.

The HRs for OS of ripretinib versus switching-adjusted BSC over time were analysed to explore the plausibility of the assumption of a lifetime treatment effect. The data for ripretinib and switching-adjusted BSC was analysed in 26-week sections up to 130 weeks. These hazard ratios and accompanying confidence intervals are presented in Table 1, along with the HR for the full observed period of 145 weeks. Over time the confidence intervals decrease as the ripretinib patient numbers increase. There is a large decrease in HR from 26 weeks to 52 weeks due to a significantly higher number of ripretinib patients being included in the analysis. Beyond 52 weeks, the HR gradually approaches the HR used in the original analysis ([redacted]) as more ripretinib patients are included. This analysis shows that the HR is consistently less than 1 and decreases with greater patient numbers for the observed trial period, indicating a significant treatment effect of ripretinib and supporting the assumption of a lifetime treatment effect.

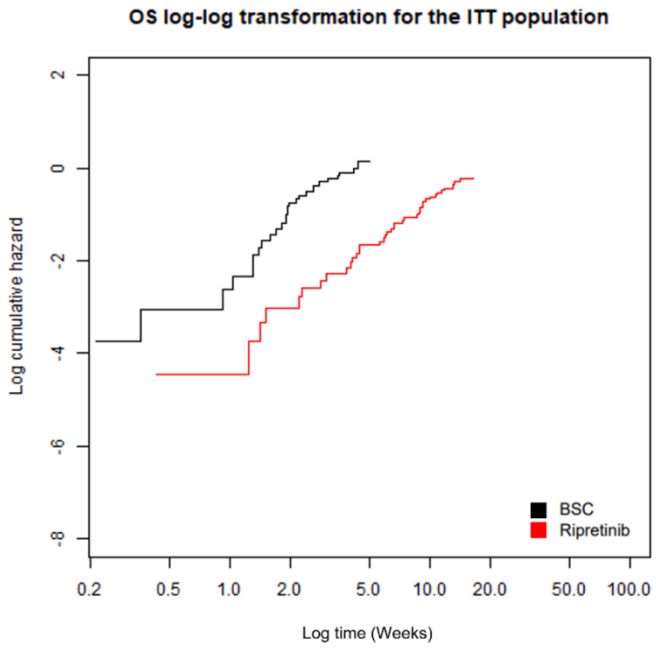
Table 1: HRs for OS of ripretinib versus switching-adjusted BSC over time

Time period	Hazard ratio	Lower 95% confidence interval	Upper 95% confidence interval	BSC patients included	Ripretinib patients included
26 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
78 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
104 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
130 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full observed period (up to 145 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care.

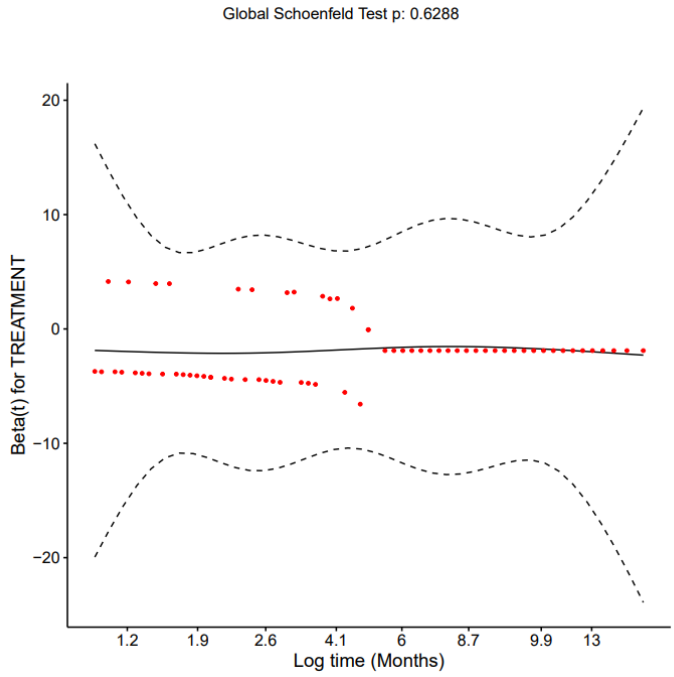
Statistical tests were also carried out to test if the proportional hazards (PH) assumption holds between the ripretinib and BSC arms of INVICTUS within the observed trial period. The results of the OS complementary log-log plot can be seen in Figure 2 and the results of the Schoenfeld residuals test can be seen in Figure 3. Inspection of these plots suggests that it would be reasonable to accept the PH assumption within the observed trial follow-up period. This is because the log-cumulative hazards for ripretinib and BSC do not cross and remain relatively parallel over time. The Schoenfeld residuals plot shows an approximate zero slope, and the p-value is >0.05 (0.6288) thus not rejecting the hypothesis of time independent residuals. It is then assumed that the PH assumption holds for the unobserved period and there is no evidence against a non-proportional treatment effect.

Figure 2: OS cumulative log-log plot



Abbreviations: BSC – Best supportive care.

Figure 3: OS Schoenfeld residuals plot



OS for both ripretinib and BSC is restricted by the risk of death from all-cause mortality in the CEM. Within the company's base case analysis this restriction impacts the OS curve for ripretinib to a greater extent because the upper bound of all-cause mortality

comes into effect earlier on in the model time horizon than on the OS curve for BSC. Therefore, a constant survival advantage over the model time horizon is not assumed for ripretinib, which is a conservative assumption in this analysis.

An analysis of the HRs for OS of post-progression adjusted ripretinib versus switching-adjusted BSC over time is presented in Table 2. Similar to the analysis that Table 1 presents, the HRs are consistently decreasing and less than 1, indicating a significant treatment effect of ripretinib and supporting the assumption of a lifetime treatment effect for ripretinib even when an adjustment is made to account for post-progression treatment. The HR of [redacted] at 12 weeks should be interpreted with caution however due to the low sample size of ripretinib patients. The increased HR of [redacted] at 24 weeks (versus [redacted] at 36 weeks) is due to the full cohort of BSC patients being included at this timepoint, whilst only [redacted] ripretinib patients are included.

Table 2: HRs for OS of post-progression adjusted ripretinib versus switching-adjusted BSC over time

Time period	Hazard ratio	Lower 95% confidence interval	Upper 95% confidence interval	BSC patients included	Ripretinib patients included
12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full observed period (up to 145 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care.

HRQoL parameters

B9. The model applies utility values for the progression-free and post-progression states of [redacted] and [redacted], respectively, based on EQ-5D-5L assessments in INVICTUS which have been mapped to the EQ-5D-3L.

(a) The post-progression utility value is very similar to the progression-free value. Please comment on why this might be the case.

(b) Please comment on whether the EQ-5D-5L data collection mechanism in INVICTUS might be subject to potential informative censoring. On average, how long after progression were the post-progression EQ-5D assessments?

(c) Please provide information on the mean EQ-5D-5L utility value and number of observations for each trial cycle and for the final treatment visit. Please present these data split by treatment group and whether the patients are still on treatment.

(d) Please provide estimates of overall mean EQ-5D for the following states: progression-free (PF) on treatment, PF off treatment, progressed disease (PD) on-treatment, and PD off-treatment.

a) The similarity between the post-progression utility value and the progression-free utility value can be attributed to the high proportion of patients treated with ripretinib post-progression ([redacted]). Treatment-specific health state utility values demonstrate that patients on treatment with ripretinib have improved QoL compared with patients on BSC alone (Table 4). The UK clinician's clinical experience with ripretinib in the Phase 1 study and the CUP was that patients were symptomatic due to their disease but those on treatment with ripretinib experienced a QoL benefit.

   As a high percentage of patients remained on treatment post-progression, these patients experienced continued QoL benefit due to ripretinib treatment, despite disease progression, contributing to the higher than expected PD utility value. Additionally, [redacted] patients ([redacted]) in the BSC arm crossed over to treatment with ripretinib upon disease progression; therefore, would have experienced some QoL benefit attributable to ripretinib treatment despite disease progression.

b) As the INVICTUS trial was for advanced-stage disease and used PFS as the primary end point, it is possible that informative censoring may have occurred. However, in the double-blind phase of the study, the number of patients that discontinued treatment due to AEs was comparable between treatment arms

([redacted] patients ([redacted]) in the placebo arm and [redacted] patients ([redacted]) in the ripretinib arm) (4). The comparable safety of treatment arms indicates that informative censoring due to increased toxicity of the intervention arm is likely to be minimal.

The average time between progression and post-progression EQ-5D assessments was [redacted] days.

c) The mean EQ-5D-5L value and number of observations for each cycle and the final treatment visit, split by whether patients were on or off treatment, and treatment arm, is provided in Table 3. As stated in response to question B9.a, patients on treatment with ripretinib have a higher utility compared to those in the same health states on treatment with BSC.

Table 3: Mean EQ-5D-5L utility value and number of observations for each trial cycle and for final treatment visit

Cycle	Ripretinib (on treatment)		BSC (on treatment)		Ripretinib (off treatment)		BSC (off treatment)	
	Number of observations (N)	Utility	Number of observations (N)	Utility	Number of observations (N)	Utility	Number of observations (N)	Utility
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

25 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29 (crossover)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; NA – Not applicable.

d) The overall mean EQ-5D utility values mapped from EQ-5D-5L to EQ-5D-3L using the algorithm from Van Hout et al. 2012 (5) for PF on treatment, PF off treatment, PD on-treatment, and PD off-treatment are provided in Table 4, both treatment-specific and for all INVICTUS patients. The analysis indicates utility values are higher for patients on treatment with ripretinib.

Table 4: EQ-5D-3L utility values for progression-free (PF) on treatment, PF off treatment, progressed disease (PD) on-treatment, and PD off-treatment.

Treatment arm	Treatment status	Utility value	
		Progression-free (PF)	Progressed disease (PD)
Ripretinib	On treatment (N=[redacted])	[redacted]	[redacted]
	Off treatment (N=[redacted])	[redacted]	[redacted]
BSC	On treatment (N=[redacted])	[redacted]	[redacted]
	Off treatment (N=[redacted])	[redacted]	[redacted]
All patients	On treatment (N=[redacted])	[redacted]	[redacted]
	Off treatment (N=[redacted])	[redacted]	[redacted]

N represents the number of observations

Abbreviations: BSC – Best supportive care; PD – Progressed disease; PF – Progression-free.

B10. The model does not include any adjustment of utility values for increasing age. Please clarify why this has not been included in the model. Please update the model to include age-adjusted utility values using a multiplicative approach based on general population EQ-5D estimates reported by Hernandez Alava *et al.* (2022).

Age-adjusted utilities have now been incorporated into the model traces, as per the general population EQ-5D estimates reported by Hernandez Alava *et al.* (2022). A switch has been added in cell D13 of the Quality of Life Inputs sheet to allow to user to turn age-adjustment of utilities on or off.

Cost parameters

B11. CS, Section B.3.5, page 98. The model includes compliance and relative dose intensity (RDI) estimates of [redacted] and [redacted], respectively, based on the double-blind period of INVICTUS.

(a) Please comment on whether applying both of these parameters together will underestimate drug costs (i.e., does RDI not already include compliance?).

(b) Please provide estimates of compliance and RDI for the whole trial period, including post-progression ripretinib use (note – the EAG would suggest that overall RDI should be calculated according to the dosing applied in the double-blind phase, i.e., at a planned dose of 150mg QD).

[Response already provided on 24th June]

B12. CS, Section B.3.5, page 97. Drug acquisition costs are calculated as a function of half-cycle corrected PFS, the cost of ripretinib per day, the number of days per cycle, compliance and RDI. This approach ignores drug wastage. Please comment on whether this omission was intentional. If this was not intentional, please amend the model.
[Response already provided on 24th June]

B13. CS Section B.1.2, Table 2, page 13. Table 2 states that additional monitoring is required for patients with a history of high blood pressure or heart conditions. Please comment on whether these additional costs are captured in the modelled costs. Please amend the model to include these additional costs, if necessary.
[Response already provided on 24th June]

Executable model

B14. The EAG has identified several apparent minor programming errors in the company's executable model. Please investigate each of the following issues, confirm if each is an error and provide an updated version of the executable model including all necessary corrections.

(a) Model, worksheet "Data Store", cells D120:E220. The model uses life tables for the UK rather than England. Life tables for England should be used.
An updated version of the CEM has been uploaded to NICE docs.

(b) Model, worksheet "Data Store", cells F120:F220. The general population mortality risk calculations assume that men and women have different risks of death at each age x, whilst also assuming that the same proportion of men and women will apply in each model cycle. Both assumptions cannot simultaneously be true. The EAG believes it would be more appropriate to use a weighted survival model (i.e., generate general population survival models for men and women and weight them by the proportion of men/women only at baseline).
An updated version of the CEM has been uploaded to NICE docs.

(c) Model, worksheet “Data Store” cells K222:K1535. These calculations calculate the risk of general population death in each model cycle. However, the lookup function is referring to values for age x+1 year rather than age x. For example, the calculation in cell H180 shows that the estimated risk of death for an individual who has survived up to age 60 is ~~0.00052125~~ 0.000505. However, the first 13 model cycles use an estimate of ~~0.000566~~ 0.000546, which is the risk for an individual who has already survived up to age 61.
An updated version of the CEM has been uploaded to NICE docs.

(d) Model, worksheet “Clinical Inputs” cells I69:I589 and L69:L589. These formulae apply a constraint which determines whether the risk of death with the disease is greater than or equal to the risk of death in the general population. If the condition is met, the value returned is the cumulative survival probability from the unadjusted OS survival function. The EAG 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).
An updated version of the CEM has been uploaded to NICE docs.

(e) Model, worksheet “Clinical Inputs”, cells E69:F589. No constraint has been applied to the PFS function. At a minimum, a logical consistency constraint should be applied to ensure that the cumulative PFS probability can never be higher than the cumulative OS probability.
An updated version of the CEM has been uploaded to NICE docs.

(f) Model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, all subsequent calculations dependent on cells I9:K10. The half-cycle correction has been applied inappropriately as the first interval is counted 1.5 times.
No action taken. Cycle 0 represents the first model cycle. Year 1 represents cycles 0-12 (13 in total). Deleting the contents of row 9 would result in only 12 cycles in year 1, but 13 in all other subsequent years.

(g) Model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, cells C9:C22. The year is rounded down to the nearest integer value in all cycles in the first year, but is not rounded down in any subsequent cycles. This will impact on discounting. The EAG would prefer not to round down the discounting multipliers, but even if this approach is preferred by the company, it should be consistent across all model cycles.
An updated version of the CEM has been uploaded to NICE docs.

(h) Model, worksheet “Results”, cell E10:E11. Life years gained (LYGs) have been discounted. The EAG believes that it is more informative to report undiscounted LYGs as these are the values which will inform discussions around the End of Life (EoL) criteria.
An updated version of the CEM has been uploaded to NICE docs.

(i) Model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, column C. Each cycle is assumed to be 1/13 years in duration. The calculations in this column assume that there are 52 weeks in a year. However, there are approximately 52.17 weeks in a year. The model should consistently deal with time units throughout.
An updated version of the CEM has been uploaded to NICE docs.

(j) Model, worksheet “Survival analysis” cells D61:AP593. The survivor functions in this worksheet define the time unit *t* as 1/13th of a year. Please confirm that this same time unit was used in the underlying time-to-event data when fitting parametric survival models (i.e., was each unit of time *t* defined as 28.0962 days? Or was it defined as 28 days, or months?).
Each time unit was defined as 28 days, representing approximately 1/13th of a year. The discrepancy between 28 days and 1/13th of a year is unlikely to have a material impact on the survival analysis and subsequent ICER.

(k) Model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, cells S10:S528. The discount rate multiplier is only being applied to the latter part of the cost calculation – extra brackets are needed.
An updated version of the CEM has been uploaded to NICE docs.

(l) Model, worksheets “Trace (Ripretinib)” and “Trace (BSC)”, column AE. The EoL cost has not been discounted in either group.
An updated version of the CEM has been uploaded to NICE docs.

(m) Model, worksheet “Model Parameters”. Independent beta distributions are used to sample health state utilities. As the values for both states are similar, this allows logically inconsistent samples whereby the utility value for PF is higher than that for PD in some samples. It would be more appropriate to apply a disutility approach which can handle ordered data, e.g., the approach described by Ren *et al.*, *PharmacoEconomics*, 2018, vol. 36).
An updated version of the CEM has been uploaded to NICE docs.

Section C: Additional analysis requests

C1. Please provide a Kaplan-Meier plot of time to treatment discontinuation in the ripretinib arm of INVICTUS (including those who continued ripretinib treatment beyond progression), including numbers of patients at risk. Please fit parametric survival models to the available time-to-event data and select a preferred model using the approach described in Decision Support Unit Technical Support Document 14.

As described in response to question A2, the company is only seeking reimbursement up to progression, whereas INVICTUS trial patients received ripretinib beyond progression. Therefore, use of this population for time to treatment discontinuation data is not relevant to the decision problem and would bias the analysis against ripretinib.

C2. Please provide Kaplan-Meier plots of post-discontinuation survival in the ripretinib group. Please provide Kaplan-Meier plots of post-progression survival in both groups (unadjusted for switching).

As described in response to question A2, the company is only seeking reimbursement up to progression, whereas INVICTUS trial patients received ripretinib beyond progression. Therefore, the analyses requested are not relevant to the decision

problem. Post-discontinuation survival analyses and unadjusted post-progression survival analyses would not be a realistic representation of the survival impact on UK patients based on expected ripretinib use and would therefore bias the analysis against ripretinib.

C3. For PFS and OS, please provide plots of the empirical/unsmoothed and smoothed hazard function for the data used in the analysis. Please also plot the hazard function of each of the parametric survival models on top of the empirical and smoothed hazard.

It was decided that extrapolation with independent survival curves was most appropriate for use within the cost-effectiveness analysis. This decision was based on assessment of log-cumulative hazard plots and the Schoenfeld test.

The log-normal distribution was chosen for the base-case for ripretinib and BSC PFS as it provided a good visual fit to the observed trial data and a good statistical fit as assessed by AIC. The observed ripretinib PFS hazard function (Figure 4) indicates that the hazard of progression is increasing between 0 and approximately 20 weeks, before fluctuating and then beginning a slow increase between 40 and 70 weeks. The shape of the observed hazard aligns well with the extrapolated hazard function for the log-normal distribution, thus supporting the parametric curve chosen to extrapolate ripretinib PFS in the base-case analysis.

The observed BSC PFS hazard function indicates that the hazard of progression is increasing between 0 and approximately 5 weeks, before declining briefly and then beginning a steep increase up to approximately 8 weeks (Figure 5). After 8 weeks, only 8 patients remain at risk and hence the tail of the hazard function should be interpreted with caution. The shape of the observed hazard aligns well with the extrapolated hazard function for the log-logistic, log-normal, and generalised Gamma distributions for up to approximately 5 weeks. The observed hazard after 5 weeks increases rapidly, which is not clinically plausible. The generalised gamma and log-normal distributions follow the observed hazard most closely whilst remaining clinically plausible beyond 5 weeks. The log-normal distribution is a more conservative approach since it models a higher hazard of progression for BSC than the generalised Gamma distribution, thereby favouring BSC over ripretinib.

The log-normal distribution was chosen for the base-case for ripretinib and BSC OS as it provided a good visual fit to the observed trial data and a good statistical fit as assessed by AIC.

Figure 6 presents the smoothed, unsmoothed, and extrapolated hazard functions for OS of ripretinib. The observed ripretinib OS hazard function indicates that the hazard of death is increasing between 0 and approximately 40 weeks. The shape of the observed hazard function aligns well with the extrapolated hazard function of the Weibull, log-logistic, log-normal and generalised Gamma distributions. After 40 weeks, the hazard function begins to curve away, indicating the hazard is beginning to plateau. Out of all seven parametric distributions, the log-normal distribution (the curve chosen to extrapolate ripretinib OS within the base-case analysis) demonstrates the most similar shape, thus supporting the base-case choice.

The observed BSC OS hazard function indicates that the hazard is increasing between 0 and approximately 7 weeks (Figure 7). The shape of the observed hazard function aligns well with the extrapolated hazard function of the Weibull, log-logistic, log-normal, and generalised Gamma distributions. After approximately 7 weeks, the hazard function gradually declines. The log-logistic and log-normal distributions also model this decline. The log-normal distribution was chosen since it more closely fits the observed BSC OS hazard function.

Figure 4: Smoothed, unsmoothed, and extrapolated hazard functions for PFS of ripretinib

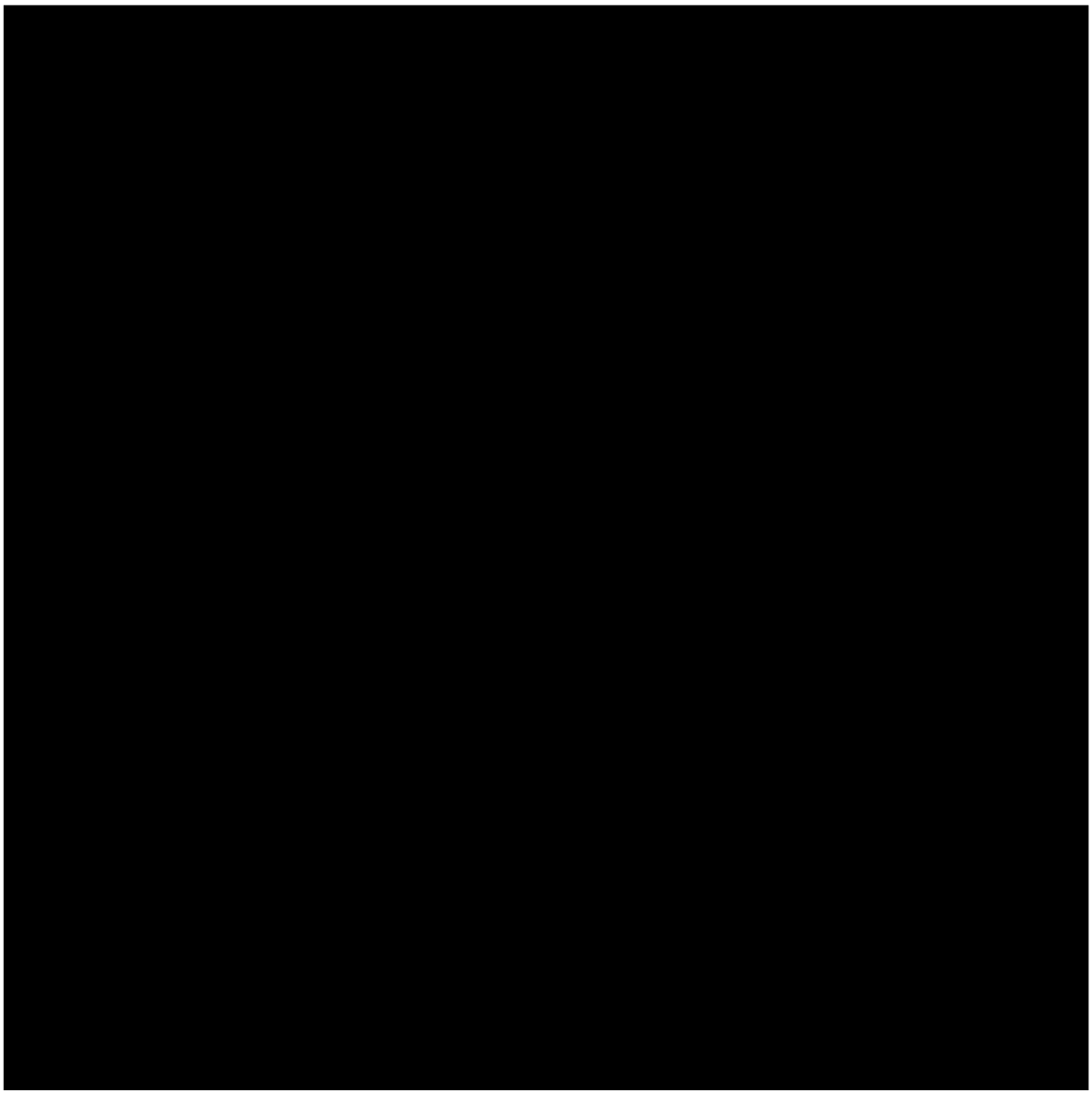
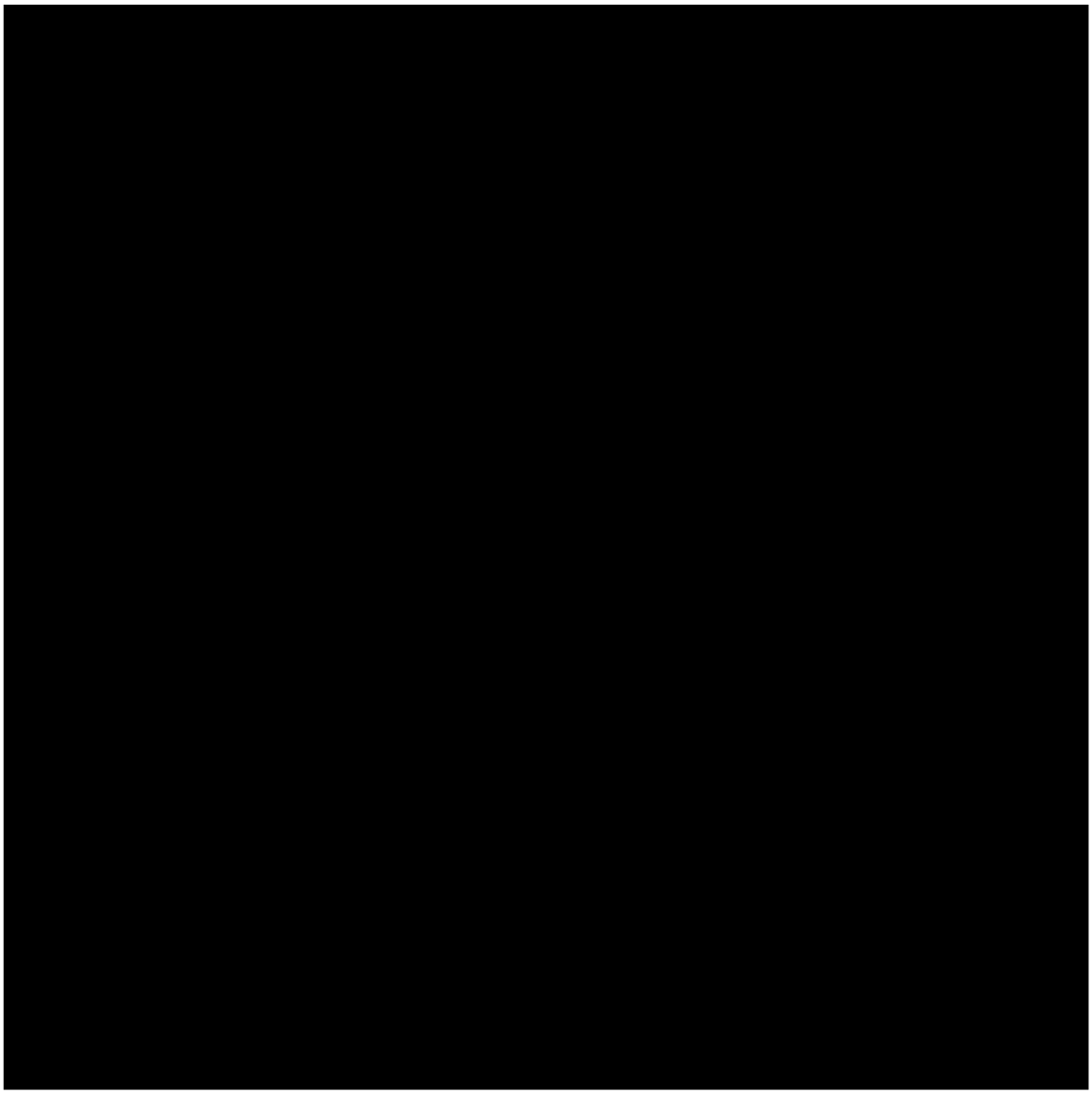


Figure 5: Smoothed, unsmoothed, and extrapolated hazard functions for PFS of BSC



Abbreviations: BSC – Best supportive care.

Figure 6: Smoothed, unsmoothed, and extrapolated hazard functions for OS of ripretinib

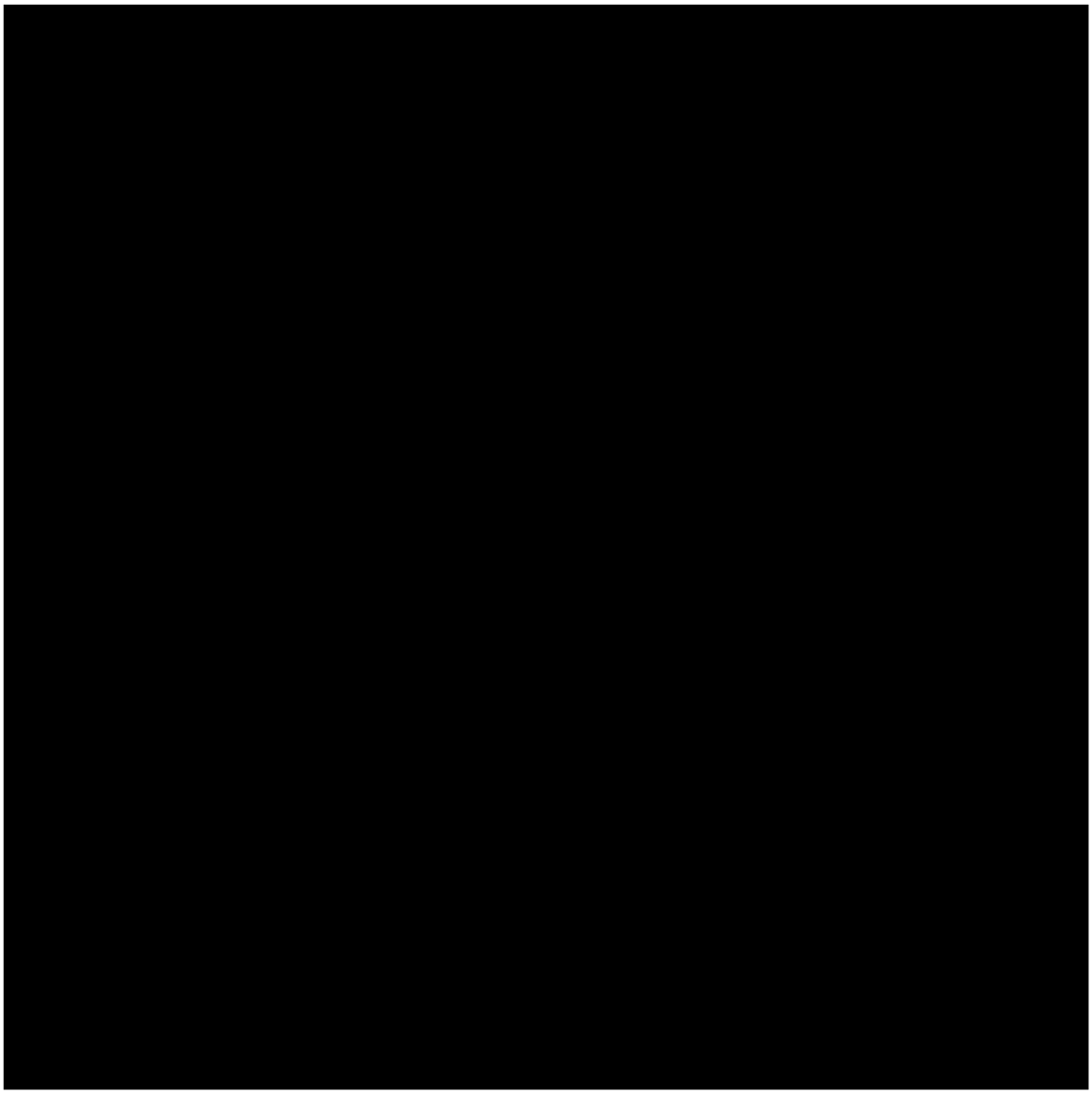
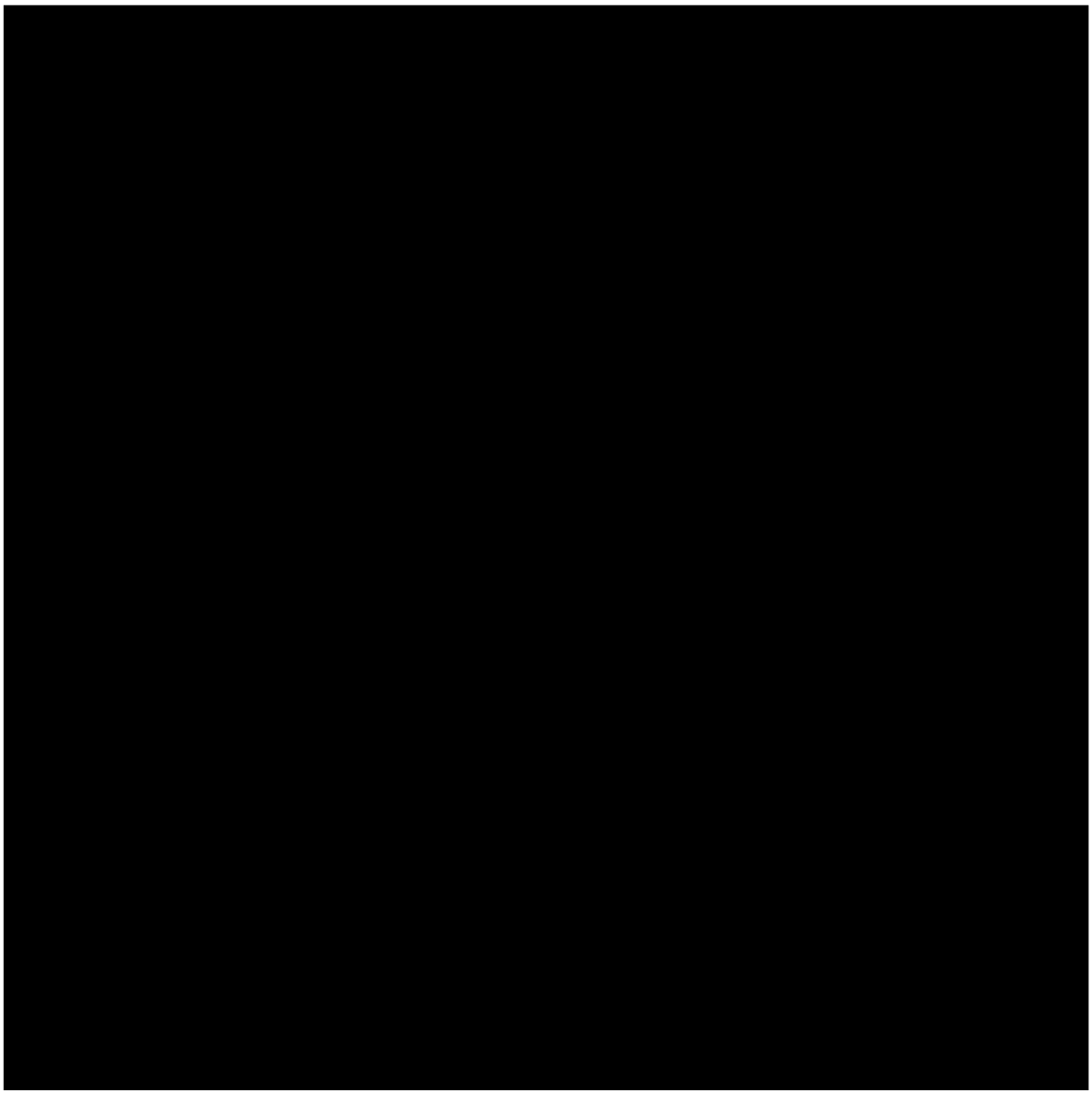


Figure 7: Smoothed, unsmoothed, and extrapolated hazard functions for OS of BSC



Abbreviations: BSC – Best supportive care.

C4. If it is the company's intention is to seek a positive NICE recommendation only in patients who have not yet progressed on ripretinib, please provide an extended switching analysis which adjusts for potential confounding associated with the continued use of post-progression ripretinib in the INVICTUS trial. If this is what has already been done in the scenario analysis labelled "Simple two-stage with recensoring" in CS Table 45, this question can be ignored.

[Response already provided on 24th June]

C5. The EAG has received clinical advice suggesting that patients who have failed three prior therapies might continue to receive regorafenib beyond disease progression. Please provide an exploratory economic analysis comparing ripretinib versus continued regorafenib at fourth-line.

[Response already provided on 24th June]

References

1. Janku F, Razak ARA, Chi P, Heinrich MC, Mehren M von, Jones RL. Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib | Journal of Clinical Oncology. Journal of Clinical Oncology. 2020;38(28):3294–303.

2. Zalcberg JR, Heinrich MC, George S, Bauer S, Schöffski P, Serrano C, et al. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. The Oncologist. 2021;26(11):e2053–60.

3. Zalcberg JR, Heinrich MC, George S, Bauer S, Schöffski P, Serrano C, et al. Clinical Benefit of Ripretinib Dose Escalation After Disease Progression in Advanced Gastrointestinal Stromal Tumor: An Analysis of the INVICTUS Study. The Oncologist. 2021 Jul 27;9999:1–11.

4. Deciphera Pharmaceuticals. A PHASE 3, INTERVENTIONAL, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF DCC-2618 IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS WHO HAVE RECEIVED TREATMENT WITH PRIOR ANTICANCER THERAPIES (INVICTUS) CLINICAL STUDY REPORT. 2019.

5. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Aug;15(5):708–15.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Additional clarification questions

July 2022

File name	Version	Contains confidential information	Date
ID3805 ripretinib additional clarification questions to PM for company_06Jul22_v3.0	**3.0**	**Yes**	**06/07/2022**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Additional clarification questions

1. **The ERG received an updated version of the model along with the first batch of clarification responses on the 27th June. This seems to include some, but not all, of the amendments that the company says they have done in the batch 2 response to question B14. Can the company confirm that the file called 'ID3805 ripretinib clarification response CEM (UK update) 27062022KM [ACIC].xlsm' is what the company considers to be their fully corrected version of the model?**

   The company does not consider this to be the fully corrected version of the CEM. The company has provided two versions of the CEM to accompany each batch of ERG questions-
   1) Partially corrected version provided on 24th June 2022 (compliance and RDI corrections only): "QINLOCK_CEM (UK update)__24Jun22_v6.2_ACiC_with PAS.xlsm"
   2) Fully corrected version provided on 1st July 2022: "QINLOCK_CEM (UK update)__01Jul22_v7.0_ACiC_with PAS.xlsm"

2. **In response to question C3, the company has provided hazard plots. Can the company please confirm that the empirical and modelled hazards reflect the base case analysis (i.e., including switching**

adjustment in the placebo group and no adjustment in the ripretinib group)?

The company can confirm for the placebo group the empirical and modelled hazards reflects simple two-stage adjustment with recensoring as per the company base case.

The company would like to correct the figure provided OS in the ripretinib group. Figure 1 presents corrected the smoothed, unsmoothed, and extrapolated hazard functions for OS of the unadjusted ripretinib data. The observed ripretinib OS hazard function indicates that the hazard of death is increasing between 0 and approximately 40 weeks. After 40 weeks, the hazard function begins to curve away, indicating the hazard is beginning to plateau. The shape of the observed hazard function aligns well with the extrapolated hazard function of the log-logistic, log-normal and generalised Gamma distributions. The log-normal distribution (the curve chosen to extrapolate ripretinib OS within the base-case analysis) provides the most conservative estimate out of these three extrapolations for the majority of the observed time period, thus supporting the base-case choice.

Figure 1: Smoothed, unsmoothed, and extrapolated hazard functions for OS of ripretinib

3. **The company has provided a table of TEAEs of special interest. Can the company please confirm that this relates to the double-blind period, and not the open-label period as stated in the table header?**
   Yes, the company can confirm the TEAEs of special interest relate to the double-blind period, not the open-label period as stated in the table header.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	GIST Cancer UK (Registered Charity No. 1129219) (GCUK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	GIST Cancer UK (GCUK) is a registered charity (No. 1129219) formed in April 2009 to provide support and progress research for patients diagnosed with Gastrointestinal Stromal Tumours. We are a network of GIST cancer patients & carers working with leading GIST specialists & National/International groups, to promote best practice. We exist to help GIST patients and their families come to terms with living with GIST cancer and we raise funds to: • Stimulate and fund GIST research. • Support Patients living with GIST cancer • Provide Information for GIST patients and their clinicians • Raise awareness of GIST cancer We receive no government funding and are run by a board of, currently ten volunteer trustees who have a close association and experience of GIST cancer, accompanied by further special volunteers with a similar connection and a variety of skills to offer the charity. All of the GIST cancer research projects that we sponsor are funded through donations and fundraising from our patients and their families. We receive some funds from pharmaceutical companies (currently from*, Blueprint Medicines & Deciphera*) which is used to assist with hosting regional and more recently, virtual patient meetings and to provide information and educational literature which has been prepared by expert GIST patients in tandem with GCUK's medical advisory board, directly to patients and via hospitals throughout the UK. GCUK is not a membership organisation. Each year we engage with over a thousand GIST patients and carers, both newly diagnosed and longer-term survivors, via:

	• our telephone helpline, • regional and virtual patient carer meetings, • PAWS-GIST clinics, • our private online patient forum • social media Facebook, Twitter, LinkedIn and Instagram platforms • our websites www.gistcancer.org.uk & www.pawsgistclinic.org.uk This amounts to many thousands of patient and carer experiences since the charity was formed in 2009. In the past couple of years during the pandemic, we have seen a significant increase in the number of GIST patients registering with our charity. Patients have felt extremely isolated and frightened and have been urgently seeking help. Joining our community has helped them enormously.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	Yes. In the past 12 months we have received grant funding of £7,000 from Deciphera which we have used to partly fund our first virtual online patient meetings and printing and postage of educational leaflets to patients and hospitals throughout the UK as described above in Section 4a.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	GCUK has gathered information about the experiences of patients since becoming a charity in 2009. We engage with GIST patients, clinicians and researchers both in the UK and internationally to further our understanding of GIST cancer and identify research opportunities or ways to support approval of new treatment options. GIST Cancer UK has played a key role in the development and implementation of infrastructure in the UK to support GIST cancer patients, including development of: • The National GIST Guidelines • The National GIST Tissue Bank • The PAWS-GIST clinic at Addenbrookes hospital in Cambridge. Through our work to support GIST patients we gain valuable information about patient experiences. GCUK engages directly with patients in a variety of ways; our private listserve (email forum community) for patients and carers, patient and carer meetings, PAWS-GIST clinics and via our telephone helpline. We have seen the evidence presented at numerous GIST conferences in mainland Europe, USA & UK showing the results of clinical trials of ripretinib, which describe it as being a therapy targeting multiple primary and secondary mutations in gastrointestinal stromal tumours, that it has a favourable safety

	profile, and that it has significantly improved progression-free survival results in GIST patients previously treated with all approved therapies. To understand more about ripretinib first-hand, we put a call out to our patient email forum asking GIST patients using ripretinib to contact us. We have interviewed a selection of GIST patients who have been using Ripretinib from between seven to sixteen months and have submitted two of these as patient experts who wish to participate in the NICE appraisal.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Many GIST cancer patients manage, with effective treatment, to live relatively normal lives, continuing to work and play as best they can while manging the side effects of treatment. In many patients their GIST cancer is found early and before it has spread, they have it removed while still small and it does not return. Depending on the extent of disease, surgery can involve quite drastic interventions such as removal of the stomach. Often the disease has reached an advanced stage prior to diagnosis, limiting the potential for surgery to totally remove the cancer. Toxic side effects are also encountered from anticancer therapies, and tolerance of these side effects varies significantly. Side effects to the drug therapies currently available via NHS include hypertension, hypothyroidism, debilitating hand foot syndrome, diarrhoea, fatigue, nausea, skin rashes and so on. The list of side effects is quite extensive but with advice from oncologists, cancer nurse specialists and fellow patients we observe that these can be managed and tolerated by many patients, providing the chance to live longer and live a normal life. However, some patients do not tolerate these drug side effects and are forced to cease treatment. Additionally, existing therapies are often ineffective in halting disease progression for certain sub-groups of patients.

	Living with GIST cancer as a patient or carer is possible but every day that you wake up you hope that it was a bad dream and that it isn't real. This is a standard defence mechanism for cancer patients and their families. Learning to cope is something that you have to do and the last thing that you want to do as a carer is to give the impression that things will not be OK. You have to give your loved one hope. The traumas and horrors of living with a type of GIST cancer that does not have a treatment that works can shatter family's lives. Carers take many forms, parents, partners, siblings, children and friends, all desperate to help and save the person that they love.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers are very grateful for the treatments that are available via the NHS. Currently for GIST patients this consists of: • Surgery • Imatinib • Sunitinib • Regorafenib Unfortunately, not all GIST cancers are the same and there are many for whom the above treatments are not effective because either their primary mutation is not targeted by the above treatments or their disease metastasizes beyond the control of the above treatments. GIST patients in the UK are currently given the above options. We understand that the trials of ripretinib showed manageable tolerability and conclusive signs of activity in patients with advanced GIST which has become resistant to prior treatments. This has been corroborated by the patients who we have interviewed who have all described the side effects as being very manageable.

8. Is there an unmet need for patients with this condition?	Yes. In advanced gastrointestinal stromal tumours (GIST), there is an unmet need for therapies that target both primary and secondary KIT & PDGFRA mutations. Patients are in need of: • effective treatments when the mutations driving the GIST cancer are not targeted by the existing licenced treatments. • treatments that are effective against secondary resistance mutations that develop following treatment with prior line(s) of tyrosine kinase inhibitors. Ripretinib is a novel switch-control kinase inhibitor designed to inhibit a wide range of *KIT and PDGFRA* mutations. We consider ripretinib to be innovative in the setting of relapsed metastatic GIST. It has the potential to improve a patients' survival and quality of life. The current alternative is no treatment or best supportive care.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages of this technology are that ripretinib: • Inhibits mutations that drive resistance to currently licenced therapies in GIST • is administered orally • is well tolerated • offers GIST patients whose tumours have progressed beyond the control of current licenced therapies a further option which can prolong their lives.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with any drug there are side effects but our discussions with patients using ripretinib has concluded that they are tolerable and manageable.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The GIST patients who will benefit are those who are unfortunate to have failed the treatments that are currently available because their disease has developed resistance mutations. Ripretinib targets these mutations.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Ripretinib has been approved by: The EMA – October 2017 The FDA in America - May 2020 The PBAC in Australia - August 2021 Currently ripretinib is not available to patients in the UK.

	This is the only inequality we can see.
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

Ripretinib:

- Inhibits mutations that drive resistance to currently licenced therapies in GIST
- is administered orally
- is well tolerated
- offers GIST patients whose tumours have progressed beyond the control of current licenced therapies a further effective option which can prolong their lives.
- GIST patients in the UK deserve access to Ripretinib in the same way as GIST patients in the rest of the world.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Sarcoma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Sarcoma UK is a national charity that funds vital research, offers support for anyone affected by sarcoma cancer and campaigns for better treatments. It is the only cancer charity in the UK focusing on all types of sarcoma. It funds research into sarcoma, information and support for anyone affected by sarcoma, and campaigns for access to effective sarcoma treatments. It is entirely funded by fundraising.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We run a support line which has regular contact from GIST patients. In early 2020, we ran the largest survey of people affected by sarcoma in the UK. It had over 1,100 responses from patients and their support networks. The survey looked across the breadth of the sarcoma landscape, from awareness of sarcoma, through diagnosis, treatment, and support. This included 87 GIST patients, 33 of whom were still undergoing active treatment. There were also 18 carers or family members of GIST patients. We also maintain contact with specialist sarcoma centres to understand current treatment options and patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	GIST is the most common type of soft tissue sarcoma; it develops in the gastrointestinal (GI) tract, a long tube running through the body from the oesophagus (gullet) to the anus (back passage) and includes the stomach and intestines. Most GISTs are found in the stomach and small bowel but can occur anywhere along the GI tract. GIST patients, on the whole, are able to live normal lives, and are able to work whilst managing side effects of treatments. However, according to their carers, almost half of the patients either often, sometimes, or always have trouble taking care of themselves. According to the National Sarcoma Survey 2020, the most common symptoms and side effects were fatigue; diarrhoea; changes to hair, skin and nails; and nausea or vomiting. GIST patients said that fatigue was the side effect with the greatest impact on their life, both during and after treatment. Sarcoma diagnosis also has a significant impact on mental wellbeing. 95% of GIST patients said that diagnosis and treatment of sarcoma negatively affected their overall mental health or emotional wellbeing.

	Caring for someone with GIST takes a large toll in many ways, including mentally, financially, and socially. Carers performed a number of tasks for the GIST patients, including providing emotional support; accompanying on trips and appointments; transporting and travelling with the patient; and communicating on behalf of the patient. Several of the respondents spent more than 50 hours a week proving care and support. As a result, well over half of the carers had to stop working or studying, either temporarily or permanently. 71% of carers said they had experienced a negative financial impact as a result of the patient's sarcoma diagnosis. Further to this, every carer (100%) said that they have felt either more often or constantly depressed or anxious since the GIST diagnosis.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are 3 main treatments available for GIST patients with advanced disease: • Imatinib • Sunitinib • Regorafenib Some treatments are more or less effective dependent on mutations within the tumour. However, there is a significant population who do not have an effective treatment either because the treatment does not target their mutation, or progression renders the treatment ineffective. Further to this, it is common for patients to stop responding to treatments. For a very small handful of patients with NTRK positive tumours, larotrectinib has just been approved for use via the Cancer Drugs Fund. This is welcomed by the patient community, but they also recognise that this is a very small population. Patients are frustrated by a lack of effective treatment options for GISTs, and the treatment options available often have severe side-effects, leading to many to require a lower (and less effective) dose.

8. Is there an unmet need for patients with this condition?	There is an unmet need in this population. There are still many for whom the current lines of treatment do not work effectively, cause serious side effects, or both. This medicine would provide them with an effective life-extending treatment.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients make it clear that having access to an increased number of kinder, more effective therapies would be welcomed.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	n/a

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with mutations which we know do not respond well to existing treatments.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 2 August 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has stated that it was unclear whether an ITC of fourth-line ripretinib against continued use of regorafenib was possible. Section 1.3, Page 11: "The ERG believes that the comparison requested at the clarification stage should be explored by the company. However, it is unclear whether reliable data are available to inform an indirect treatment comparison (ITC)."	Change the statement to reflect the fact that a comparison between ripretinib and post-progression regorafenib is highly unlikely to be possible.	An indirect treatment comparison (ITC) between ripretinib and post-progression regorafenib was explored but was found not to be feasible due to the low proportion of fourth-line patients in the most appropriate trial that studied regorafenib in the fourth line. As stated in the original CS Appendix D.7.1, Table 4, Page 18, Kang 2021 studied avapritinib vs. regorafenib in the fourth-line However, only 68/476 (14.3%) patients were fourth-line patients.[1] A second trial, Serrano 2019, studied regorafenib in the fourth line. However, as stated in the original CS Appendix D.7.1, Table 4, the sample size was very small (n=14), and the study investigated alternation of sunitinib and regorafenib which makes it unsuitable for an ITC of ripretinib against regorafenib alone.	This is not a factual inaccuracy. The CS does not clearly state that the company explored the feasibility of an ITC of ripretinib versus continued regorafenib. However, the ERG agrees that Kang and Serrano may not be sufficient to inform an ITC. The ERG has amended the text to state that it is unlikely that sufficient data are available to inform an ITC. Similar wording has been applied in other sections of the report.

Issue 2 Uncertainty surrounding the level of HRQoL experienced by patients after progression on fourth-line therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states that utilities from the GRID trial are	The company believes that the higher utility values derived from the INVICTUS	In the GRID trial, the majority (113/199 [56.8%]) of patients had received only 2 previous lines of anticancer therapy and were	This is not a factual inaccuracy – it is a difference of opinion. The ERG's main concern regarding the INVICTUS EQ-5D

appropriate for progressed disease. Section 1.5, Page 15: "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."	trial are appropriate and plausible, and that use of utility values from the GRID trial is inappropriate.	therefore receiving third-line therapy[2], compared to the proposed 4th line therapy position of ripretinib. Use of utility values from a previous line of therapy are not appropriate as the populations are not comparable and this would underestimate the incremental QALYs for ripretinib.	data is that they are unadjusted for post-progression ripretinib use and therefore are unlikely to reflect post-progression utility for patients receiving BSC alone. The ERG's clinical advisors shared this concern. The ERG notes that the published model reported by Liao *et al.* also used utility values from the GRID trial. The ERG report has not been amended.

Issue 3 Patients who continue to receive regorafenib post-progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states that "some" patients continue to receive regorafenib post-progression. Section 3.3, Page 25: "The company's clarification response (question A3) agrees that some patients continue to receive regorafenib beyond disease progression."	The following amendments to the text are proposed: "The company's clarification response (question A3) agrees that ~~some~~ **a minority** of patients continue to receive regorafenib beyond disease progression and **only if a patient's radiological progression is limited, if they continue to tolerate the therapy, and while the patient continues to have clinical benefit**."	UK clinical opinion was sought as to whether the use of ripretinib would be continued following progression. The clinician advised treatment would generally be stopped at clear/aggressive progression. However, for heavily pre-treated GIST patients, an exception may be made if radiological progression is limited, and the patient is tolerating the therapy. In such cases, treatment would continue while the patient continues to have clinical benefit. This is expected to be the case for a minority of GIST patients and would only occur when no alternative treatment option is available.	This is not a factual inaccuracy. The ERG's clinical advisors commented that some patients continue to receive regorafenib after progression. One clinical advisor suggested that this is around 50% of patients who progress on third-line regorafenib, whilst the other advisor suggested that the vast majority of patients continue on regorafenib, at least for some period of time. The ERG also notes that there are no other alternative treatment options currently available after patients have progressed on regorafenib. The ERG further notes that the proportion of ripretinib patients receiving post-progression ripretinib in INVICTUS was 49% at the May

			2019 cut-off, and will likely be higher at later cut-offs.

Issue 4 Missing references

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.4.2, Page 44, Table 11. The table is missing a reference to the EMA's assessment report on ripretinib.[3] "Source: Blay et al. 2020,10 supplementary appendix, Table S2; von Mehren et al. 2019, presentation at ESMO (abstract LBA87 and poster)."	The following amendments to the text are proposed: "Source: Blay et al. 2020, 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.**"	Some of the data is taken from the EMA's assessment report on ripretinib.[3]	The ERG agrees. The report has been amended as requested.
Section 4.4.4, Page 45, Table 12. The table is missing a reference to Gelderblom et al. 2020. "Source: von Mehren et al. 2019, presentation at ESMO."	The following amendments to the text are proposed: "Source: von Mehren et al. 2019, presentation at ESMO; **Gelderblom et al. 2020, presentation at CTOS Virtual Meeting (poster).**"	Some of the data is taken from a poster presented at the 2020 CTOS Virtual Meeting by Gelderblom et al.[4]	
Section 4.4.5, Page 46: The statement is missing references. "Grade 3 or 4 TEAEs reported in ≥5% of patients in the ripretinib	The following references should be added to the statement: "Source: Gelderblom, H. et al. Clinical benefit with ripretinib as ≥fourth-line treatment in	These data are taken from a poster presented at the 2020 CTOS Virtual Meeting by Gelderblom et al.[4]	

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 ([redacted] vs. [redacted]), and hypophosphataemia ([redacted] vs. [redacted]).”	patients with advanced gastrointestinal stromal tumor: Update from the phase 3 INVICTUS study. (2020).		

Issue 5 Sensitivity analyses for survival analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG incorrectly states parametric models other than those stated in scenario analyses were not explored Section 5.3.5, Page 89, Part (4) (f) “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 **Error! Reference source not found.**). Other models are not explored.”	To update the text as follows: “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 **Error! Reference source not found.**). Other models are not ~~explored~~ **reported but are options in the Excel-based model submitted to NICE and reviewed by the ERG**.”	The statement that other models were not explored is inaccurate since the model has switches in cells D14, D15, D37 and D38 of the Clinical Inputs sheet which allow the exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma models to be explored. The results for the best-fitting models were reported in the CS.	This statement was intended to refer to the results of scenario analyses which are presented in the CS. The ERG believes the report is already clear that the model includes other survival distributions as these have been included in the ERG’s exploratory analyses. For clarity, the text has been amended to read *“Other models are not explored in the CS.”*

Issue 6 Hypertension disutility

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.4, Page 64: "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. The justification for this is unclear."	To update the text as follows: "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. ~~The justification for this is unclear.~~"	Document B (Section B.3.4, Adverse reactions, page 94) submitted to NICE states that disutility values were identified in a previous NICE submission for GIST (TA10523) and a NICE submission for colorectal cancer (TA439). This is where the disutility for hypertension was sourced from, in which the disutility is 0.069 and the source is stated to be Doyle *et al.* (2008). Therefore, it is clear why a disutility of 0.069 was used for hypertension.	The text has been amended to read *"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 footnotes to Table 19 have also been amended.

Issue 7 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.1.2, Page 52 (third paragraph) "The economic analyses included the company's review used a variety of modelling approaches, including state transition, partitioned survival and simulation models."	To update the text as follows: "The economic analyses included **in** the company's review used a variety of modelling approaches, including state transition, partitioned survival and simulation models.	Typographical error.	All typographical errors have been corrected as suggested.

Section 5.2.1, Page 53: BSC is not defined in the list of abbreviations beneath Table 15. "GIST - gastrointestinal stromal tumour; mg - milligram; QD - once a day; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services"	To update the text as follows: "GIST - gastrointestinal stromal tumour; mg - milligram; QD - once a day; **BSC - best supportive care**; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services	Typographical error.	
Section 5.2.4, Page 57, sub-heading Time-to-event parameters, Statistical adjustment of OS data to account for treatment switching: "The decision to remain on ripretinib (at either the current or increased dose), was informed by the investigator's viewof whether the patient was receiving benefit from ripretinib, and if dose escalation could be tolerated (see clarification response,[2] question B3)."	To update the text as follows: "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)."	Typographical error.	
Section 5.2.4, Page 58, sub-heading Time-to-event parameters, Adjustment of	To update the text as follows "The CS[1] reports the results of scenario analyses using six methods of statistical	Typographical error.	

<table>
<tr>
<td>OS data in the placebo group

“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 including the simple two-stage approach, the complex two-stage approach and the RPSFTM; each approach was applied separately with and without re-censoring.”</td>
<td>adjustment of OS data to account for treatment switching from placebo to ripretinib. These ~~including~~ include the simple two-stage approach, the complex two-stage approach and the RPSFTM; each approach was applied separately with and without re-censoring.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Section 5.2.4, Page 65, Table 20:

The BSC costs for pain management in the progression-free state are incorrectly stated to be £17.03.</td>
<td>To update the text as follows (taken from Document B, Section B.3.5, Intervention and comparator costs and resource use, Table 33, page 99):

<table>
<tr><td>BSC costs (pain management), PF state (per 28-day cycle)</td><td>~~£17.03~~ £17.35</td></tr>
</table>
</td>
<td>Typographical error.</td>
<td></td>
</tr>
<tr>
<td>Section 5.3.5, Page 88, second bullet:

“With respect to the ripretinib group, the clinical advisor also commented that the company’s selected log-logistic model</td>
<td>To update the text as follows:

“With respect to the ripretinib group, the clinical advisor also commented that the company’s selected ~~log-logistic~~ log-normal model (the solid red line in Error! Reference source not found.) appears to be optimistic for fourth-line treatment and that the exponential and Weibull</td>
<td>Typographical error.</td>
<td></td>
</tr>
</table>

(the solid red line in **Error! Reference source not found.**) appears to be optimistic for fourth-line treatment and that the exponential and Weibull models (the solid blue and orange lines in **Error! Reference source not found.**) reflect *"a more plausible situation.""*	models (the solid blue and orange lines in **Error! Reference source not found.**) reflect *"a more plausible situation.""*		
Section 5.4.1, Page 96: "**EA5: ERG preferred analysis** The ERG's preferred analysis includes all amendments included in EAs 1-5."	To update the text as follows: "**EA5: ERG preferred analysis** The ERG's preferred analysis includes all amendments included in EAs 1-**4**."	Typographical error.	

Issue 8 ACiC marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Section 1.4, Page 12	TEAEs of special interest included squamous cell carcinoma (SCC) of the skin ([redacted] and actinic keratosis ([redacted]).	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%]). As requested by NICE, these data from the CSR have been published previously and may be unmarked in the	All marking has been amended as requested

<table>
<tr><td></td><td></td><td>ERG report for transparency. These data have been published in CADTH's reimbursement recommendation for ripretinib.[5]</td><td>by the company</td></tr>
<tr><td>Section 4.4.2, Page 44</td><td>The overall frequency of treatment-emergent adverse events (TEAEs) was similar for ripretinib and placebo (99% vs 98%), whilst drug-related TEAEs were [redacted] ([redacted] vs. [redacted]). 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 [redacted] ([redacted] vs. [redacted]). Serious AEs (SAEs) were less frequent for ripretinib (31% vs. 44%), whilst drug-related SAEs were [redacted] ([redacted] vs. [redacted])</td><td>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%).

These data are already published in the EMA's assessment report on ripretinib.[3]</td><td></td></tr>
<tr><td>Section 4.4.2, Page 44, Table 11</td><td>Table 1: Summary of TEAEs in the double-blind phase of INVICTUS, safety population (adapted from CS Table 15)
<table>
<tr><th>Categories</th><th>Ripretinib (n=85), n (%)</th><th>Placebo (n=43)*, n (%)</th></tr>
<tr><td>All AEs</td><td></td><td></td></tr>
<tr><td>Any TEAE</td><td>84 (98.8%)</td><td>42 (97.7%)</td></tr>
<tr><td>Any drug-related TEAE</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Any grade 3/4 TEAE</td><td>42 (49.4%)</td><td>19 (44.2%)</td></tr>
<tr><td>Any grade 3/4 drug-related TEAE</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>Table 2: Summary of TEAEs in the double-blind phase of INVICTUS, safety population (adapted from CS Table 15)
<table>
<tr><th>Categories</th><th>Ripretinib (n=85), n (%)</th><th>Placebo (n=43)*, n (%)</th></tr>
<tr><td>All AEs</td><td></td><td></td></tr>
<tr><td>Any TEAE</td><td>84 (98.8%)</td><td>42 (97.7%)</td></tr>
<tr><td>Any drug-related TEAE</td><td>72 (84.7)</td><td>26 (60.5)</td></tr>
<tr><td>Any grade 3/4 TEAE</td><td>42 (49.4%)</td><td>19 (44.2%)</td></tr>
</table></td><td></td></tr>
</table>

Any treatment-emergent SAE	26 (30.6%)	19 (44.2%)
Any treatment-emergent drug-related SAE	[redacted]	[redacted]

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)

These data are already published in the EMA's assessment report on ripretinib.[3]

Section 4.4.4, Page 45, Table 12

Table 3: 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%)	[redacted]	10 (23.3%)	[redacted]

Table 4: 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)*
Any TEAE or Grade 3/4 TEAE**	84 (98.8%)	42 (49.4%)	42 (97.7%)
Alopecia	44 (51.8%)	0	2 (4.7%)
Fatigue	36 (42.4%)	3 (3.5%)	10 (23.3%)
Nausea	33 (38.8%)	3 (3.5%)	5 (11.6%)
Abdominal pain	31 (36.5%)	6 (7.1%)	13 (30.2%)

Nausea	33 (38.8%)	[redacted]	5 (11.6%)	[redacted]
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%)	[redacted]	3 (7.0%)	[redacted]
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

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

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%)	[redacted]	0	[redacted]
Lipase increased	9 (10.6%)	[redacted]	0	[redacted]
Pruritus	9 (10.6%)	0	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

These data are already published in a poster presented at the 2020 CTOS Virtual Meeting by Gelderblom et al.[4]

<table>
<tr><td></td><td><table><tr><td>Stomatitis</td><td>9 (10.6%)</td><td>0</td><td>0</td><td>0</td></tr></table></td><td></td><td></td></tr>
<tr><td>Section 4.4.5, Page 46</td><td>The most common Grade 3 or 4 laboratory abnormalities (≥4%) were anaemia (9% vs. 14%), increased lipase ([redacted] vs. [redacted]), and hypophosphataemia ([redacted] vs. [redacted]).</td><td>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%).

These data are already published in a poster presented at the 2020 CTOS Virtual Meeting by Gelderblom et al.[4]</td><td></td></tr>
<tr><td>Section 4.4.6, Page 46, Table 13</td><td>TEAEs of special interest are shown in Error! Reference source not found.. Squamous cell carcinoma (SCC) of the skin occurred in [redacted] in the ripretinib arm and [redacted] in the placebo arm, whilst actinic keratosis (dry, scaly patches of sun-damaged skin which can progress to skin cancer) occurred in [redacted] in the ripretinib arm and [redacted] in the placebo arm.</td><td>TEAEs of special interest are shown in Error! Reference source not found.. 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.

These data have been published in CADTH’s reimbursement recommendation for ripretinib.[5]</td><td></td></tr>
<tr><td>Section 4.4.6, Page 46, Table 13</td><td>Table 5: TEAEs of special interest in double-blind period, safety population (reproduced from company’s clarification response, question A12)<table><tr><th>Preferred term</th><th>Ripretinib (n=85), n (%)</th><th>Place</th></tr><tr><td>Squamous cell carcinoma of skin</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Actinic keratosis</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Table 6: TEAEs of special interest in double-blind period, safety population (reproduced from company’s clarification response, question A12)<table><tr><th>Preferred term</th><th>Ripretinib (n=85), n (</th></tr><tr><td>Squamous cell carcinoma of skin</td><td>2 (2.4)</td></tr><tr><td>Actinic keratosis</td><td>5 (5.9)</td></tr></table></td><td></td></tr>
</table>

		These data have been published in CADTH's reimbursement recommendation for ripretinib.[5]	
Section 4.9, Page 50	The most common Grade 3 or 4 TEAEs were anaemia (9% vs. 14%); abdominal pain (7% vs. 5%); hypertension (7% vs. 0%); increased lipase ([redacted] vs. [redacted] and hypophosphataemia ([redacted] vs. [redacted]). TEAEs of special interest included SCC of the skin ([redacted]) and actinic keratosis ([redacted]).	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%]). These data have been published in a poster presented at the 2020 CTOS Virtual Meeting by Gelderblom et al. and CADTH's reimbursement recommendation for ripretinib.[4,5]	
Section 7, Page 103	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 ([redacted]) and actinic keratosis ([redacted]).	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%]).	

		These data have been published in CADTH's reimbursement recommendation for ripretinib.[5]	

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

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Contributions of authors

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

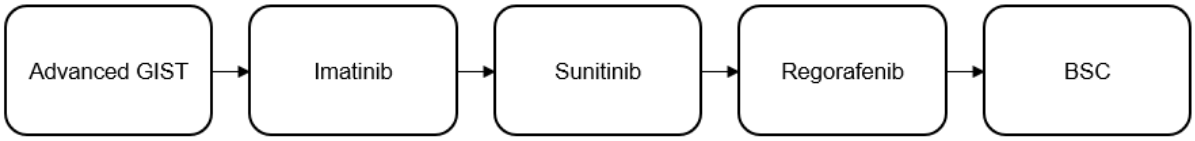
2.2.1 Primary localised GIST: surgery and adjuvant imatinib

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)

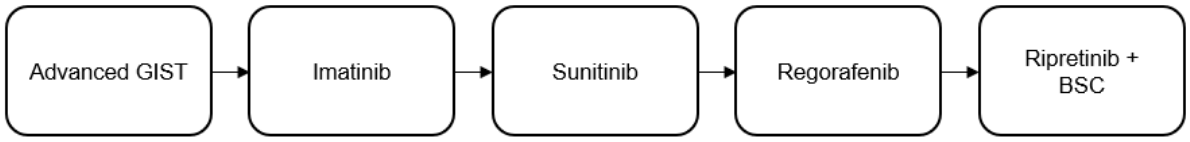


BSC - best supportive care; GIST - gastrointestinal stromal tumour

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

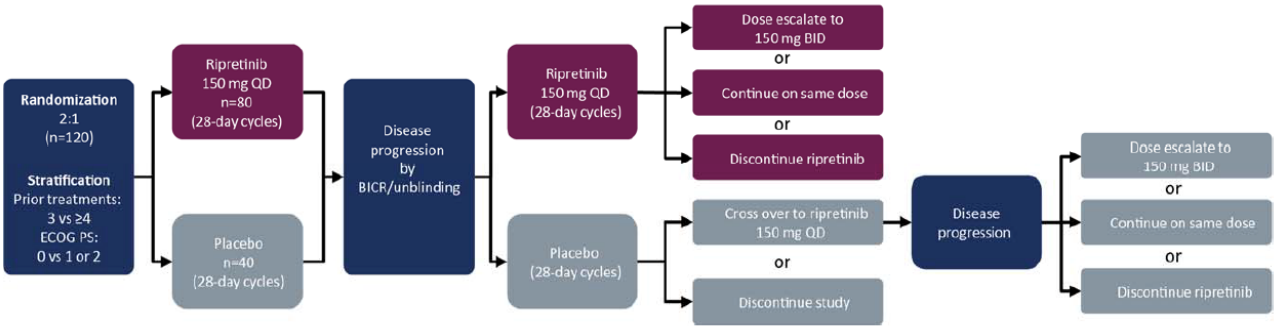
The company's SLR identified one relevant RCT of ripretinib. INVICTUS[5] is an international, multicentre, randomised, double-blind, placebo-controlled Phase 3 trial in patients with advanced GIST after at least 3 prior anticancer therapies, comparing the efficacy of ripretinib plus BSC versus placebo 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.

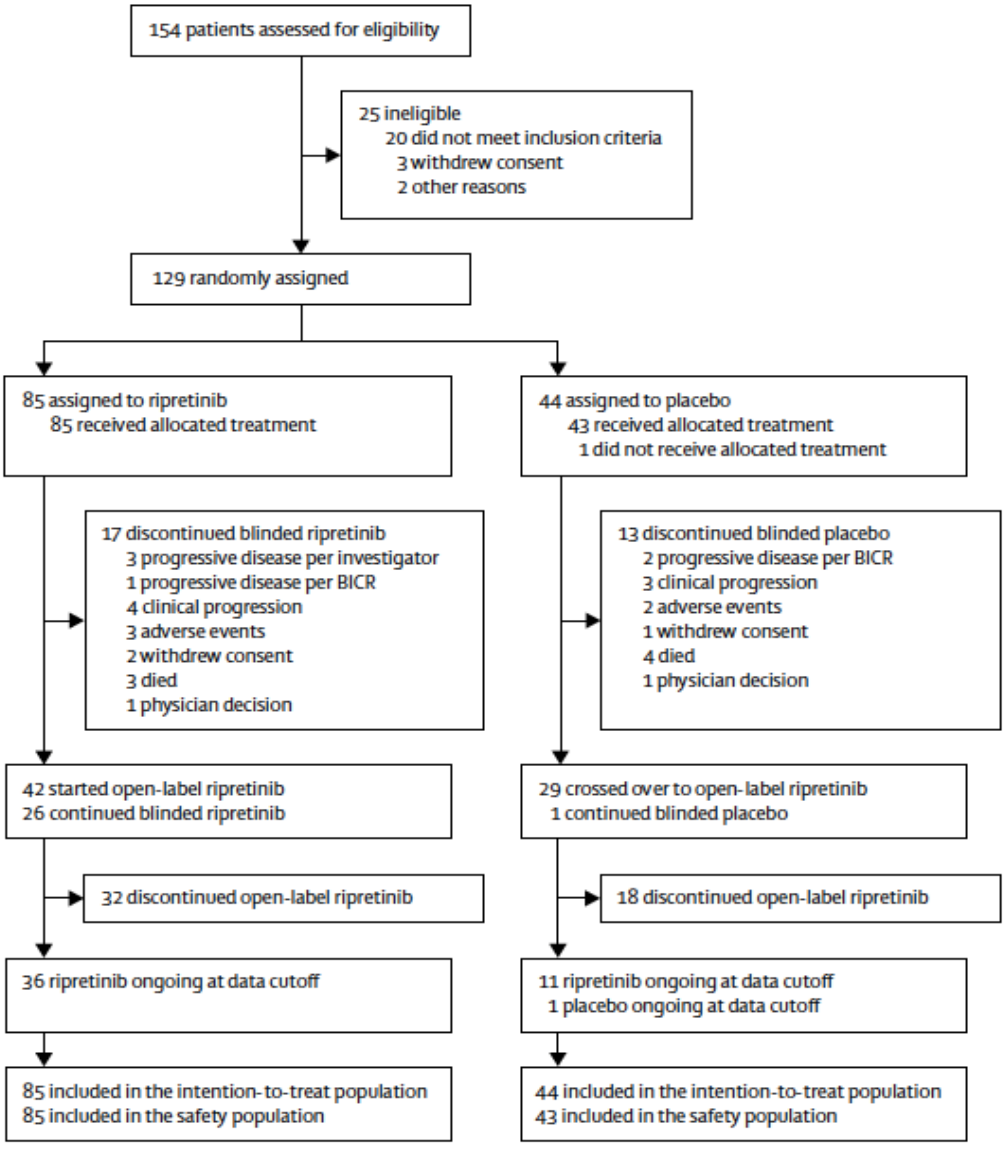
The company's clarification response[2] (question A5) provides data on patient flow for the cut-off of the 10th August 2020. At this point, 65 patients in the ripretinib group had progressed, of whom 43 dose-escalated to ripretinib 150mg BID and 22 either continued ripretinib 150mg QD or discontinued 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

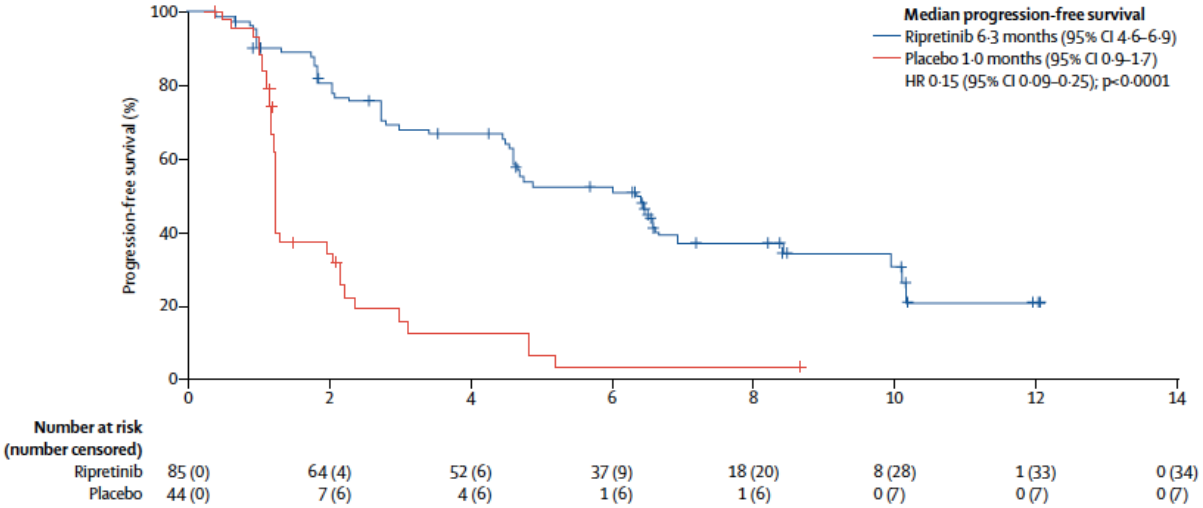
In the 43 (of 85) patients in the ripretinib group who dose escalated to ripretinib 150mg BID upon progression (Table 7), median PFS1 (time from randomisation to progression) was 4.6 months, and median PFS2 (time from first dose at 150mg BID to progression or death) was 3.7 months (CS,[1] Section B.2.7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

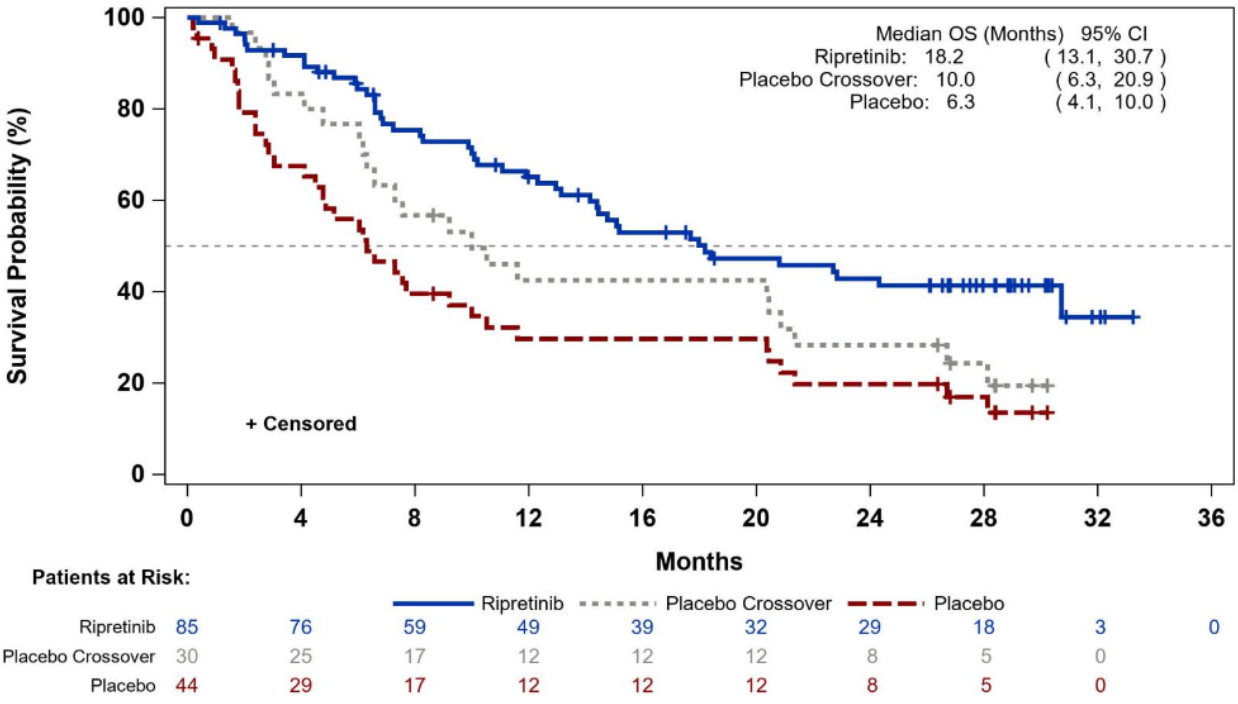
In a *post hoc* analysis, median OS in the 29 patients who crossed over from placebo to ripretinib was 11.6 months (May 2019 cut-off) or 10.0 months (January 2021 cut-off). Median OS in the 15 placebo patients not crossing over was 1.8 months (May 2019) [redacted] (January 2021 cut-off; clarification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

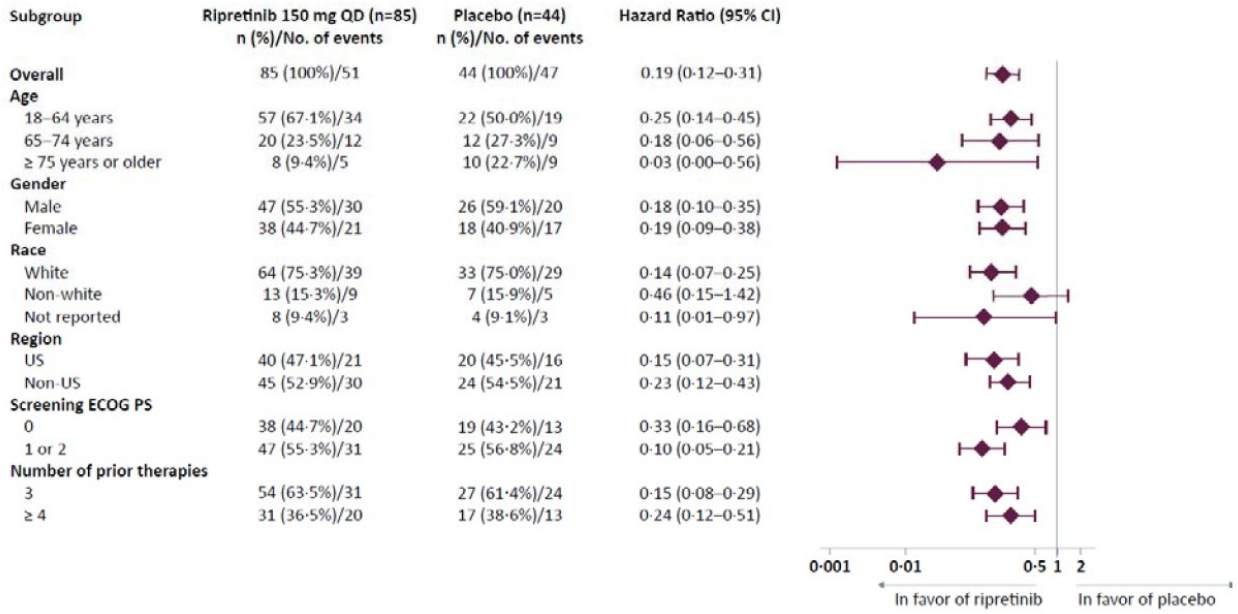
Figure 7: Kaplan-Meier plot of OS with extended follow-up, January 2021 cut-off, including placebo patients who did not switch to ripretinib (reproduced from company's clarification response, question A9)

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)

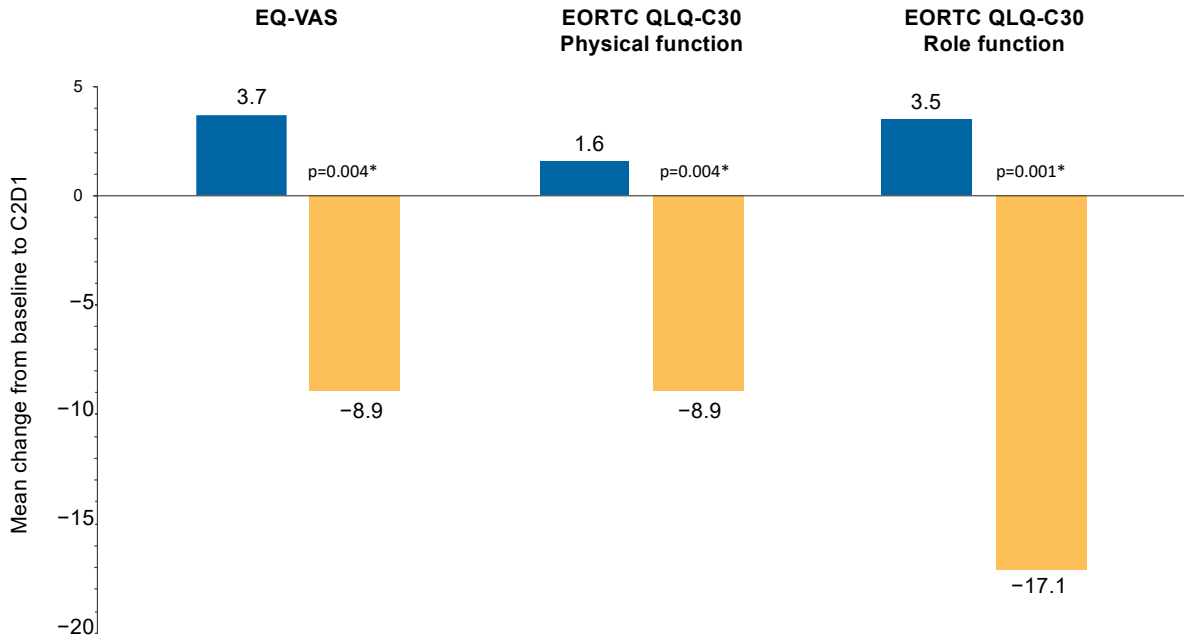
HRQoL in INVICTUS[5] was assessed using the EORTC QLQ-C30 role and physical functioning domains, the EQ-5D-5L questionnaire and the EQ-VAS (CS,[1] Section B.2.6). The ERG notes that the clinical section of the CS only reports HRQoL data from baseline to the first day of Cycle 2 (i.e., the first 29 days 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).

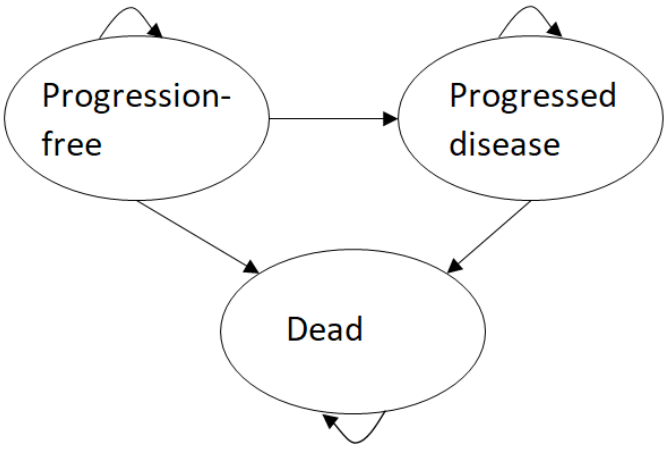
Comparators

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

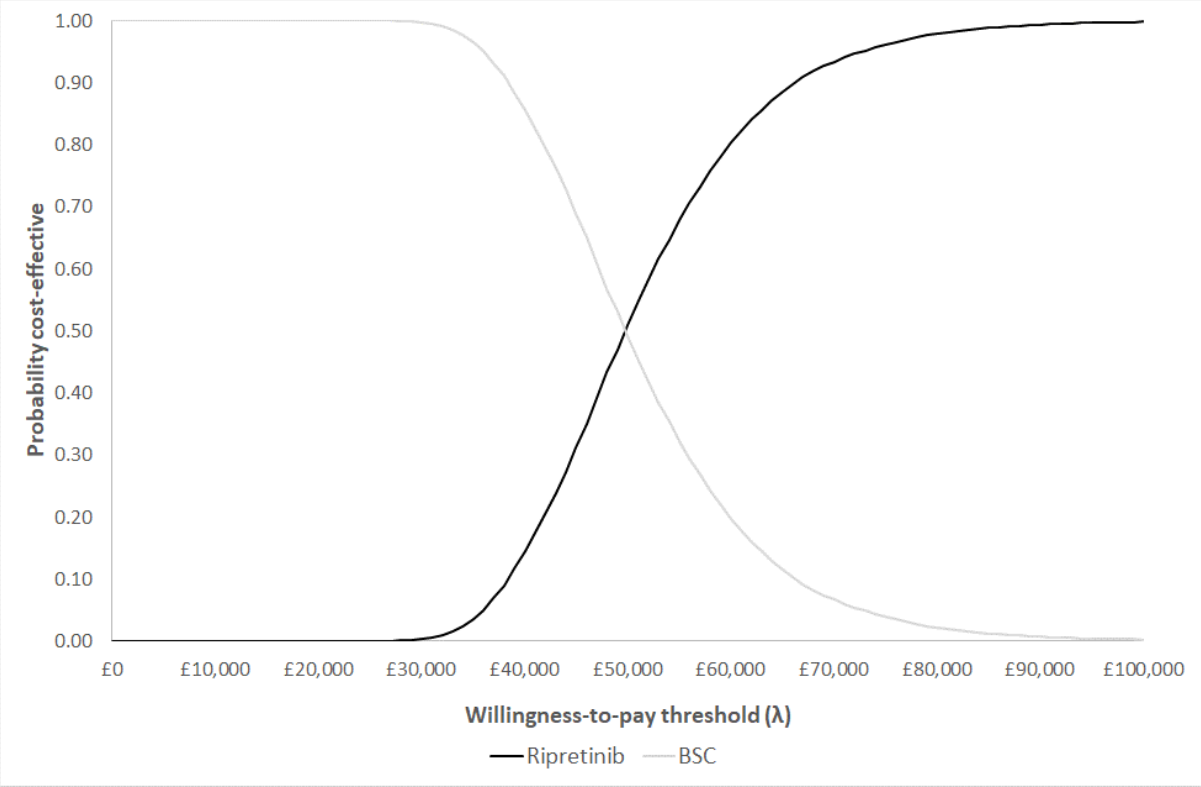
Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,610**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	
Deterministic model							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]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

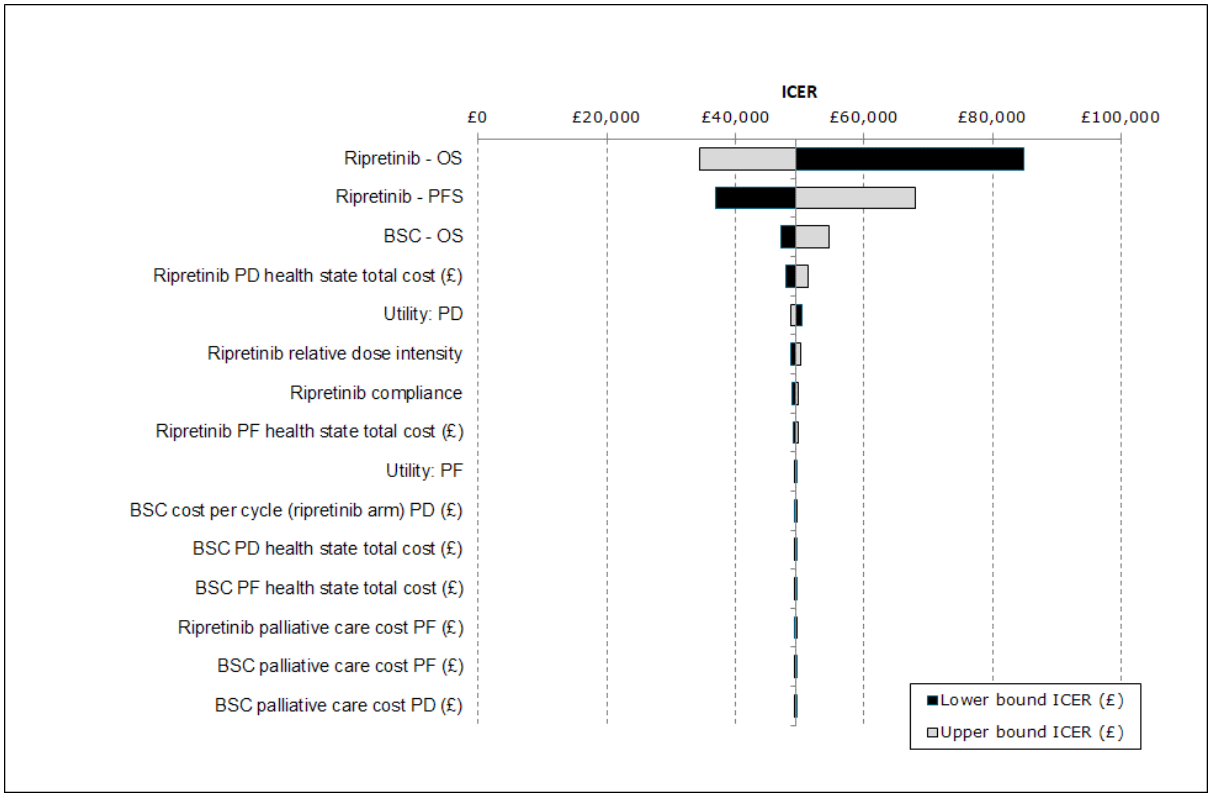


BSC - best supportive care

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

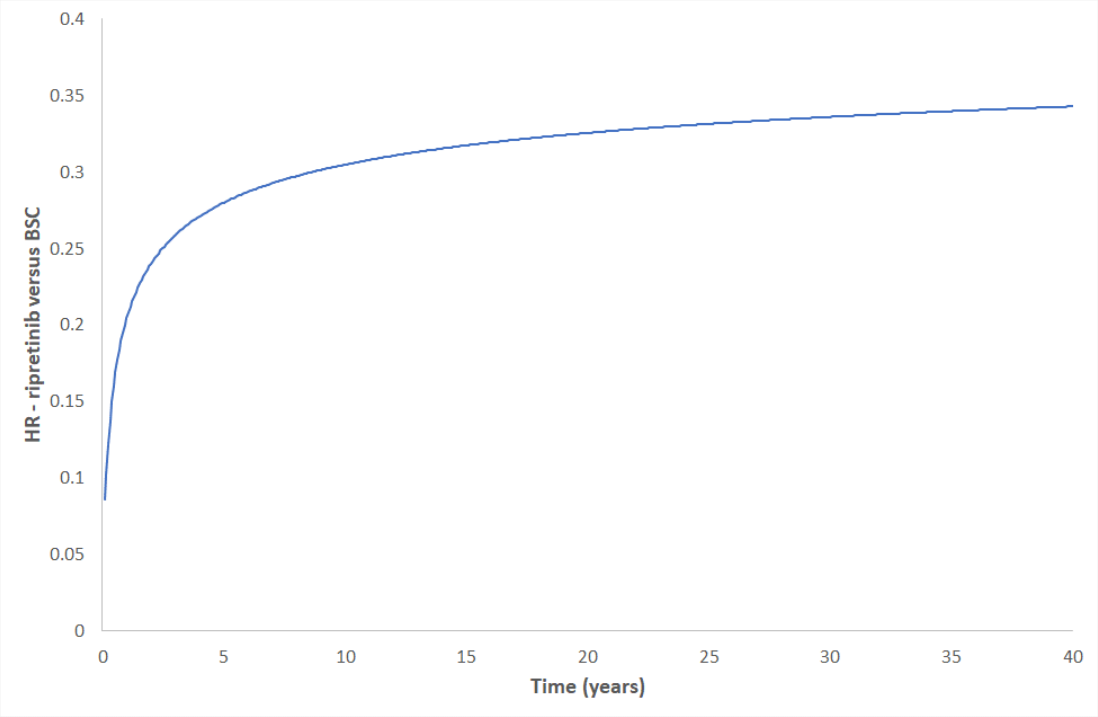
The ERG has several concerns regarding the parametric survival modelling presented in the CS.[1] These concerns are discussed below in terms of the general considerations around model fitting and selection set out in NICE DSU TSDs 14 and 21.[42, 43]

(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=[redacted])	[redacted]	[redacted]
	Off treatment (N=[redacted])	[redacted]	[redacted]
BSC	On treatment (N=[redacted])	[redacted]	[redacted]
	Off treatment (N=[redacted])	[redacted]	[redacted]
All patients	On treatment (N=[redacted])	[redacted]	[redacted]
	Off treatment (N=[redacted])	[redacted]	[redacted]

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 = [redacted]) 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.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

NICE National Institute for Health and Care Excellence

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **12 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	Josh Bedel
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Deciphera Pharmaceuticals
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	Yes	The company believes that the only appropriate comparator for ripretinib in fourth-line GIST is best supportive care (BSC). The comparison of ripretinib with BSC alone is aligned with previous NICE TAs of treatments for GIST that were the last line of therapy at the time. Both sunitinib and regorafenib (second line and third line therapy, respectively) were compared with BSC only, and were not compared against the previous line of therapy (imatinib and sunitinib, respectively)(1,2). In response to Issue 1 highlighted by the company in the FAC, relating to "Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression", the ERG stated that it is unlikely that sufficient data are available to inform an indirect treatment comparison (ITC) between ripretinib and regorafenib. An ITC between ripretinib and post-progression regorafenib has been considered by the company but is unlikely to be feasible due to the small numbers of fourth-line or greater patients in regorafenib clinical trials identified in the company's systematic literature review (SLR). As stated in the original CS Appendix D.7.1, Table 4, Page 18, Kang 2021 studied avapritinib vs. regorafenib in the fourth-line. However, a very small sample size of only 35/236 (14.3%) patients treated with regorafenib were fourth-line patients, with the remaining treated with regorafenib in the third-line. In INVICTUS, 54/85 (64%) patients treated with ripretinib were fourth-line patients, having received 3 prior therapies, with the remaining patients treated with ripretinib in later lines of therapy.(3,4)

		A second trial, Serrano 2019, studied regorafenib in the fourth line, in a single-arm phase 1/2 trial. The study investigated alternation of sunitinib and regorafenib which makes it unsuitable for an ITC of ripretinib against regorafenib alone.(5) In addition, as stated in the original CS Appendix D.7.1, Table 4, the sample size was very small (n=14).
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	Yes	UK clinicians at an advisory board held in August 2022 stated that they expect patients treated with ripretinib to have outcomes which are the same or better in fourth line therapy compared to those reported in INVICTUS.(6) This is further supported by subgroup analyses from INVICTUS. The HRs shown in Figure 1 represent the relative influence of treatment effectiveness based on receiving 3 or ≥4 lines of prior systemic anti-cancer therapy. The hazard ratio (HR) values for PFS are similar for 3 prior lines of therapy (HR [CI]: academic/commercial in confidence information removed') compared to ≥4 prior lines of therapy (HR [CI]: academic/commercial in confidence information removed'), and confidence intervals overlap substantially. **Figure 1: Forest plot of Progression-free Survival based on Independent Radiologic Review in Double-Blind period in Patient Subgroups (ITT population)**  Abbreviations: CI – confidence interval; DCC-2618 – ripretinib; ECOG – Eastern Cooperative Oncology Group; ITT – intention-to-treat.

Data cut-off date: 31st May 2019
Source: Deciphera Pharmaceuticals. A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study To Assess The Safety And Efficacy Of Dcc-2618 In Patients With Advanced Gastrointestinal Stromal Tumors Who Have Received Treatment With Prior Anticancer Therapies (Invictus) Clinical Study Report, 2019.(7)

The HR in the OS subgroup analysis of number of prior therapies in INVICTUS in Table 1, based on the latest 15th January 2021 data cut, and the OS Kaplan-Meier plots for subgroups by number of prior therapies are presented in Figure 2 and Figure 3, with the PFS Kaplan-Meier plots for the same subgroups presented in Figure 4 and Figure 5. In the subgroup that aligns with the decision problem (patients with 3 prior lines of therapy) there is a lower OS HR than for patients with >= 4 prior therapies.

Table 1: Subgroup analysis of number of prior therapies: Ripretinib vs placebo HR

Subgroup	Ripretinib vs Placebo HR (95% CI)
3 prior therapies (n=54)	academic/commercial in confidence information removed'
>= 4 prior therapies (n=31)	academic/commercial in confidence information removed'

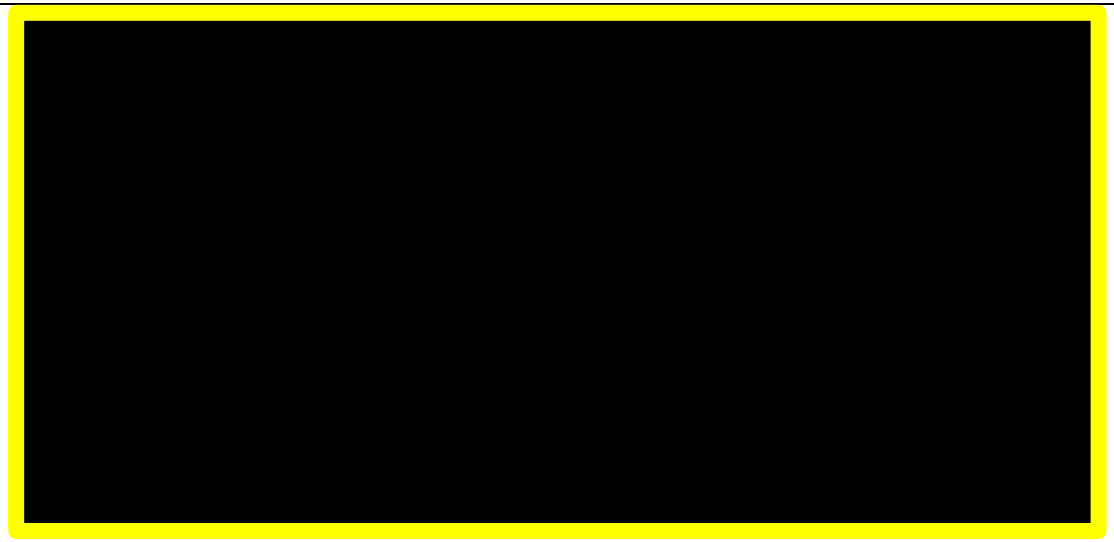
Abbreviations: CI – confidence interval; HR – hazard ratio.

Figure 2: Kaplan-Meier plot: OS, 3 prior therapies

		 Abbreviations: CI – Confidence interval; NC – Not available; NC – Not calculable. **Figure 3: Kaplan Meier plot: OS, 4 or more prior therapies**

		 Abbreviations: CI – Confidence interval; NC – Not available; NC – Not calculable. **Figure 4: Kaplan-Meier plot: PFS, 3 prior therapies**

		 Abbreviations: BSC – Best supportive care; PFS – Progression free survival. **Figure 5: Kaplan-Meier plot: PFS, 4 or more prior therapies**

		 Abbreviations: BSC – Best supportive care; PFS – Progression free survival. Therefore, by using the full INVICTUS population in the economic model, the company has made a conservative assumption with regards to efficacy of ripretinib in fourth-line GIST.
Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given	No	The company disagrees that ripretinib may result in additional survival benefit when used post-progression, since there is limited data to support this assumption. UK clinicians at an advisory board held in August 2022 were unable to predict the difference (if any) in survival in relation to INVICTUS data, if treatment was stopped at progression.(6) The ERG report stated: "it is unclear which OS adjustment method should be considered the most appropriate in the ripretinib group". The method preferred by the ERG to adjust OS in the ripretinib arm was the simple two-stage-estimation (TSE) method with re-censoring, as per the company submission.

the company's stopping rule		The simple method included time to progression as a co-variate and the complex method included time to progression, Eastern Cooperative Oncology Group (ECOG) performance status, quality of life (QoL) and age as co-variates. As time to progression was the only statistically significant co-variate and the use of co-variates in the complex model would add additional uncertainty to the analyses given the small sample size, the simple model was employed in the base-case analysis. However, the two-stage method assumes no unmeasured confounders at the point of secondary baseline. Therefore, the complex model, which includes all co-variates that are likely to be prognostic of switching and survival could also be appropriate and was explored in a scenario analysis in the company submission. Re-censoring was used to protect against informative censoring in the counterfactual dataset (the dataset had there been no post-progression ripretinib treatment). However, re-censoring causes a loss of longer-term survival information which is problematic when estimates of long-term survival effects are required, as is the case when estimating OS. Latimer et al investigated whether re-censoring should always be used in adjustment analyses and concluded that analyses should be conducted with and without re-censoring, since both methods produce biases.(8) The rank preserving structural failure time model (RPSFTM) method was ruled out because the 'common treatment effect' assumption does not hold due to the trial design of INVICTUS. Given the inherent uncertainty regarding the type of two-stage adjustment to perform, the unknown direction and magnitude of resulting biases, and the fact that UK clinicians were unable to predict the difference (if any) in survival in relation to INVICTUS data if treatment was stopped at progression, the company have not included any adjustment to the ripretinib arm to account for post-progression treatment.
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	Yes	The company would like to re-iterate that reimbursement for ripretinib is being sought up to progression only. UK clinicians at an advisory board held in August 2022 stated that when considering whether to continue treatment with ripretinib, clinicians would consider the patient's best interest, taking into account clinical benefit and tolerability. The clinicians advised that treatment would be stopped at clear progression.(6) As stated in response to ERG clarification question A2b, an exception may be made for heavily pre-treated GIST patients if radiological progression is limited, and the patient is tolerating the therapy. In such cases, treatment would continue while the patient continues to have clinical benefit. This is expected to be the case for

		a minority of GIST patients and would only occur when no alternative treatment option is available. The decision to continue a patient's current treatment would be made based on scans taken at regular intervals. The frequency of these scans would depend on the hospital, but re-staging would be performed approximately every 2-3 months. If a patient is symptomatic, an earlier scan would be considered. *Limited radiological progression is defined by the UK clinician as only a limited increase in tumour size on radiology, slow radiological increase, and/or no extensive change in the size of the tumour, as well as clinical symptoms remaining manageable and/or have not increased significantly due to the limited progression.* *The UK clinician stated that clinical benefit could be due to disease control, clinical symptom control, and/or benefit or maintenance of the patients' quality of life with respect to aspects which are impacted by the disease.*
Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy	Yes	The higher-than-expected utility value for the progression-free health state from the INVICTUS trial may be attributable to the improved side effect profile of ripretinib compared with other GIST treatments, especially regorafenib. Other treatments incur higher rates of adverse events and more severe AEs than ripretinib: • Treatment-related treatment emergent adverse events of grade 3 or 4 were reported in 21 (24.7%) of the ripretinib-treated patients in the INVICTUS trial.(9) In comparison, drug-related adverse events of grade 3 or higher were reported in 81 (61.4%) of the regorafenib-treated patients in the GRID trial.(10) • One patient treated with ripretinib in the INVICTUS trial experienced a grade 5 adverse event (death, cause unknown).(4) In the GRID trial, grade 5 adverse events were reported in 7 (5.3%) of the 132 patients in the regorafenib arm. In two patients (1.5%), the grade 5 adverse events were considered by the investigator to be drug-related.(10) The superior adverse event profile of ripretinib compared with other treatments is further supported by the patient organisation submissions to NICE for this appraisal. The representative for the GIST Cancer Registry stated "We understand that the trials of ripretinib showed manageable tolerability… This has been corroborated by the patients who we have interviewed who have all described the side effects as being very manageable." The representative for Sarcoma UK reiterated this sentiment, stating "Patients are frustrated by a lack of effective treatment options for GISTs, and the treatment options available often have severe side-effects, leading to many to require a lower (and less effective) dose… Patients make it clear that having access to an increased number of kinder, more effective therapies would be welcomed."

An additional utility analysis of the INVICTUS trial has been conducted to account for the high proportion of patients receiving BSC that crossed over to ripretinib on disease progression (30/44 patients; 68%).(7) The mean EQ-5D utility value mapped from EQ-5D-5L to EQ-5D-3L using the algorithm from Van Hout et al. 2012 was calculated for patients treated with BSC in the PD health state (Table 2).(11)

Table 2: Treatment- and health state-specific utilities calculated from INVICTUS

Treatment	Health state	Number of observations	Mean utility scores (SD)
All patients	PF	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
	PD	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
BSC*	PD	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'

*Exclusive of values recorded after crossover to ripretinib
Abbreviations: BSC – Best supportive care; PD – Progressed disease; PF – Progression-free; SD – Standard deviation

EQ-5D based utility scores as per intention-to-treat (ITT) were used as the base case in the company's submitted model. UK clinicians at an advisory board held in August 2022 stated that GRID data from regorafenib is not comparable enough to ripretinib, due to substantial difference in tolerability, to use the GRID PD utility as a proxy.

In response to concerns raised by the ERG, and further consideration of the model's representation of the positioning sought by the company, the ripretinib PD health state utility value in the company's base case has

		been changed to be equal to the BSC PD utility value presented in Table 2, to reflect the fact that patients stop treatment upon progression in the model. The company believes using a lower utility value, from a population which better aligns to the modelled PD population, is more reflective of the likely benefit to HrQOL from the use of ripretinib.(6)

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Exclusion of drug wastage costs	Section 5.3.5 Main issues identified from the ERG's critical appraisal, page 93	Yes	UK clinicians at an advisory board held in August 2022 stated there would be ripretinib wastage. Patients would be closely monitored (every 28 days) in this heavily pre-treated setting. The prescription and supply would closely match the patients' level of progression so that wastage would be tightly controlled. Clinicians estimated that any wastage would affect fewer than 5% of patients.(6)

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
EA1: Correction of errors	The company's original submitted model contained a number of minor errors.	Corrections made by the ERG have been accepted and incorporated into the company's model.	Corrections decrease the company base case ICER from £49,441 to £44,677 (-£4,764).
EA3: Utility value for progressed disease state based on GRID trial plus age-adjusted utility values	The company's base case used a treatment independent PD utility of academic/commercial in confidence information removed' and no age-adjustment of utility values	The company's base case has been updated to a BSC PD utility of academic/commercial in confidence information removed' and included age-adjustment of utility values	Changes increase the corrected company base case ICER from £44,677 to £47,280 (+ £2,603).
Company's revised base case following technical engagement	Incremental QALYs: academic/commercial in confidence information removed'	Incremental costs: academic/commercial in confidence information removed'	Combined revised ICER: £47,280

Sensitivity analyses around revised base case

One-way sensitivity analyses

An OWSA diagram presenting the top 15 most sensitive parameters is presented in Figure 6, with tabulated results presented in Table 3. The model was most sensitive to the shape and scale of the ripretinib OS and PFS distributions, BSC OS distribution, and ripretinib health states costs.

Figure 6: OWSA tornado diagram

Table 3: Tabulated OWSA results

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Ripretinib - OS	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
Ripretinib - PFS	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
BSC - OS	academic/commercial in confidence	academic/commercial in confidence	academic/commercial in confidence

	information removed'	information removed'	information removed'
Ripretinib PD health state total cost (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
Utility: PD	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
Ripretinib relative dose intensity	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
Ripretinib PF health state total cost (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
Utility: PF	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
End of life cost (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
BSC cost per cycle (ripretinib arm) PD (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
BSC PD health state total cost (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
BSC palliative care cost PD (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
Ripretinib palliative care cost PF (£)	academic/commercial in	academic/commercial in	academic/commercial in

	confidence information removed'	confidence information removed'	confidence information removed'
Ripretinib palliative care cost PD (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'
BSC palliative care cost PF (£)	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'

Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; OS – Overall survival; PD – Progressed disease; PF – Progression-free; PFS – Progression-free survival.

Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSAs) were conducted to explore the impact of model parameter uncertainty on the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. Ten thousand simulations were performed, which combined give a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results. PFS and OS remained independent within the PSA as per a standard PSM. However, the sum of the proportion of patients in each health state was not able to exceed 100% of the patient population. For gender proportions, event rates, compliance, relative dose intensity and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs, a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed.

Total costs, QALYs and incremental cost per QALY gained for ripretinib versus BSC are presented in Table 4. An incremental cost-effectiveness plane scatter plot, cost-effectiveness acceptability curve, and cost-effectiveness acceptability frontier were produced to graphically illustrate the level of variability and uncertainty in the results, as shown in Figure 7, Figure 8 and Figure 9, respectively.

Table 4: PSA results for ripretinib versus BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
BSC	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	-	-	-
Ripretinib	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	academic/commercial in confidence information removed'	47,521

Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; QALYs – Quality-adjusted life years.

Figure 7: Incremental cost-effectiveness plane for ripretinib versus BSC

Figure 8: Cost-effectiveness acceptability curve for ripretinib versus BSC

Figure 9: Cost-effectiveness acceptability frontier for ripretinib versus BSC

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with advanced gastrointestinal stromal tumours or caring for a patient with advanced gastrointestinal stromal tumours. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report, section 1.1, table 1.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

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Deadline for comments by **5pm** on **12 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Part 1: Living with this condition or caring for a patient with advanced gastrointestinal stromal tumours after 3 therapies

Table 1 About you, advanced gastrointestinal stromal tumours, current treatments and equality

1. Your name Andrea Weston	
2. Are you (please tick all that apply)	x A patient with advanced gastrointestinal stromal tumours after 3 therapies? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced gastrointestinal stromal tumours? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	GIST Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) x Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	x I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference x I have not completed part 2 of the statement

6. What is your experience of living with advanced gastrointestinal stromal tumours after 3 therapies? **If you are a carer (for someone with advanced gastrointestinal stromal tumours after 3 therapies) please share your experience of caring for them**	I am able to live alongside my cancer due to the targeted therapy I receive I work part time and whilst I may not have as much energy as I had before my diagnosis I am still able to live a relatively normal life. Monthly blood tests, a telephone consultation each month and 3 monthly scans have become part of my life.
7a. What do you think of the current treatments and care available for advanced gastrointestinal stromal tumours after 3 therapies on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**I am grateful to have had another option to try in ripretinib. Second and third line treatment both failed in my case. Ripretinib has worked to stabilise my disease.** **I think patients with gist would be grateful and relieved to have another treatment option.**
8. If there are disadvantages for patients of current NHS treatments for advanced gastrointestinal stromal tumours after 3 therapies (for example, how ripretinib is given or taken, side effects of treatment, and any others) please describe these	Side effects of ripretinib include hair loss and hand-foot syndrome Bloods are closely monitored every month

9a. If there are advantages of ripretinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ripretinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**I have found ripretinib to be more tolerable than previous treatment with both sunitinib and regorafanib. Side effects are much milder. I lead a normal life and can still work, travel,exercise without too much restriction.** **I feel all of the advantages I have stated are important as I still want to lead my life alongside of my condition and not just be a cancer patient.** **Ripretinib side effects appear to be more tolerable than both second and third line treatment for gist.**
10. If there are disadvantages of ripretinib over current treatments on the NHS please describe these. For example, are there any risks with ripretinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't feel that the risks with ripretinib are any greater than the risks associated with the current treatment available.
11. Are there any groups of patients who might benefit more from ripretinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	If a patient also had heart problems then possibly they may be unsuitable for treatment with ripretinib

12. Are there any potential equality issues that should be taken into account when considering advanced gastrointestinal stromal tumours after 3 therapies and ripretinib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No I don't think so.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	
Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	

Patient expert statement

Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy We consider patient perspectives may particularly help to address this issue. Please find more information about this issue in section 5.3.5 of the ERG report.	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- My experience with ripretinib has been positive.
- This treatment has enabled me to continue living my life.
- Ripretinib in my experience is more tolerable than previous treatments.
- Ripretinib treats more mutations of gist than current targeted treatment
- Ripretinib gives hope to patients who have exhausted current treatment options.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

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- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with advanced gastrointestinal stromal tumours after 3 therapies

Table 1 About you, advanced gastrointestinal stromal tumours, current treatments and equality

1. Your name	Bradley Price
2. Are you (please tick all that apply)	☐ A patient with advanced gastrointestinal stromal tumours after 3 therapies? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced gastrointestinal stromal tumours? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Sarcoma UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with advanced gastrointestinal stromal tumours after 3 therapies? **If you are a carer (for someone with advanced gastrointestinal stromal tumours after 3 therapies) please share your experience of caring for them**	Sarcoma UK is the only UK-wide charity for all sarcoma patients.
7a. What do you think of the current treatments and care available for advanced gastrointestinal stromal tumours after 3 therapies on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**There are no currently treatments for GIST patients after 3 lines of therapy. Studies have shown that following these three treatments, patients have on average 6 weeks of life remaining.** **The current first three lines of treatment can be more or less effective dependent on mutations within the tumour. However, there is a significant population who do not have an effective treatment either because the treatment does not target their mutation, or progression renders the treatment ineffective. Further to this, it is common for patients to stop responding to treatments.** **Patients are frustrated by a lack of effective treatment options for GISTs, and the treatment options available often have severe side-effects, leading to many to require a lower (and less effective) dose.**
8. If there are disadvantages for patients of current NHS treatments for advanced gastrointestinal stromal	There are no treatments in this setting.

tumours after 3 therapies (for example, how ripretinib is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of ripretinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ripretinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**Anecdotal evidence from discussions with clinicans who took part in the UK trial for ripretinib have made it clear that it has a significantly reduced side-effect profile compared to other lines of treatment. This is significant as living with GIST has a significant impact on life.** **According to the National Sarcoma Survey 2020, the most common symptoms and side effects were fatigue; diarrhoea; changes to hair, skin and nails; and nausea or vomiting. GIST patients said that fatigue was the side effect with the greatest impact on their life, both during and after treatment.** **Sarcoma diagnosis also has a significant impact on mental wellbeing. 95% of GIST patients said that diagnosis and treatment of sarcoma negatively affected their overall mental health or emotional wellbeing.** **Caring for someone with GIST takes a large toll in many ways, including mentally, financially, and socially. Carers performed a number of tasks for the GIST patients, including providing emotional support; accompanying on trips and appointments; transporting and travelling with the patient; and communicating on behalf of the patient. Several of the respondents spent more than 50 hours a week proving care and support. As a result, well over half of the carers had to stop working or studying, either temporarily or permanently.** **71% of carers said they had experienced a negative financial impact as a result of the patient's sarcoma diagnosis. Further to this, every carer (100%) said that they have felt either more often or constantly depressed or anxious since the GIST diagnosis**
10. If there are disadvantages of ripretinib over current treatments on the NHS please describe these.	No

For example, are there any risks with ripretinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from ripretinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with mutations which we know do not respond well to existing treatments, as well as patients with wild-type GIST, who have no actionable mutation.
12. Are there any potential equality issues that should be taken into account when considering advanced gastrointestinal stromal tumours after 3 therapies and ripretinib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No
13. Are there any other issues that you would like the committee to consider?	No treatments for the whole GIST population have been available for some time, and it will be many years before another comes down the pipeline.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

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Table 2 Issues arising from ERG report

Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	Please see Sarcoma UK submission
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	Please see Sarcoma UK submission
Inappropriate assumption that post-	Please see Sarcoma UK submission

progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	Please see Sarcoma UK submission
Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy We consider patient perspectives may particularly help to address this issue. Please find more information about this issue in section 5.3.5 of the ERG report.	Please see Sarcoma UK submission

Patient expert statement

Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- GIST patients in this setting have no further treatment options and have a very limited time remaining.
- Ripretinib is the first new treatment for this group in five years and this will help extend life.
- Ripretinib is well-tolerated in patients and allows them to go about their daily lives.
- Patients want access to new treatments as existing treatments can often fail.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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Clinical expert statement and technical engagement response form

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Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

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Part 1: Treating advanced gastrointestinal stromal tumours after 3 therapies and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Charlotte Benson
2. Name of organisation	Royal Marsden Hospital
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced gastrointestinal stromal tumours? ☐ A specialist in the clinical evidence base for advanced gastrointestinal stromal tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

8. What is the main aim of treatment for advanced gastrointestinal stromal tumours after 3 therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To control disease, stop disease progression, improve disease related symptoms and quality of life, possibly to increase overall survival
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Cessation of tumour growth, decrease in tumour density on CT scan, possible decrease in tumour dimension, improvement of disease related symptoms and quality of life
10. In your view, is there an unmet need for patients and healthcare professionals in advanced gastrointestinal stromal tumours after 3 therapies?	Yes there is no treatment available in this setting except for symptomatic management/best supportive care
11. How is advanced gastrointestinal stromal tumours after 3 therapies currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The majority are treated with best supportive care/management of disease related symptoms A small group of patients that are progressing following 3 lines of treatment for GIST may be referred for early Phase trials depending on patient fitness and trial availability (although there are currently no such trials available in UK). Similarly compassionate use programmes for other TKIs may be explored when available. Yes this pathway is well defined, and clearly outlined in British Sarcoma/GIST guidelines as well as ESMO guidelines. Patients with GIST are treated in specialised centres by designated clinicians and nurses with experience of this condition and treatment pathway is broadly the same in all of these centres. Potential extra line of treatment for patients with progressive disease, allowing opportunity of disease control and symptomatic benefit as well as possibility of prolongation of survival

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes it would be used in the 4th line for patients progressing on regorafenib The clinical setting would be a designated clinic for patients with GIST in a regional Sarcoma centre with specialist nursing support. These clinics already exist for patients with GIST so no additional investments or facilities would be needed
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes- I do expect clinically meaningful benefits for patients in this situation Symptom benefit, improved progression free survival, improved overall survival, manageable side effects/AEs in the hands of experienced clinicians I have looked after a number of patients on ripretinib- either taking part in the clinical trial or as part of an expanded access programme and have found the treatment to be effective and well tolerated
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No the INVICTUS study included patients from the general population with GIST in the specified clinical groups- I would expect ripretinib to be helpful for all patients in the 4th line setting with adequate performance status and organ function
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	No this technology would be embedded within existing clinics which already have the set up in place to monitor and look after patients. Frequency of assessments and blood tests is within the expected range

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Usual starting and stopping rules for patients with advanced GIST Testing will include clinical assessment, routine blood tests and regular cross sectional imaging ie Start treatment-. patients that have progressed on imatinib/sunitinib/regorafenib that are deemed fit for treatment by experienced clinicians Stop- patients on Ripretinib who either don't tolerate the treatment or have clear evidence of clinical and radiologic disease progression as assessed by experienced clinicians
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Quality of life (QoL) improvements would be compared to best supportive care as there are no alternative treatments for this patient population The improvements in progression free survival and overall survival are likely to translate into clinical benefit for this patient particularly as side effects from Ripretinib are largely manageable. Therefore I would expect health related benefits to improve with this technology The INVICTUS study used the standard EORTC QoL measure and this remained stable in the trial in patients on active drug compared to a decrease in QoL measurements for those on placebo.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Yes this is a meaningful treatment option for patients with metastatic GIST in the 4th line setting who currently have no other treatment options and which is in my opinion an unmet need. Yes this is a significant 'step change' the first in 5 years since the licensing of Regorafenib . The completion and reporting of the Invictus Phase III study

• Does the use of the technology address any particular unmet need of the patient population?	represents a concerted effort by the GIST community worldwide for this rare disease.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects from this drug are manageable in the context of GIST clinics run by specialist clinicians with dedicated nursing support and patient information. A number of the common side effects including fatigue, diarrhoea, hypertension and palmar plantar erythema are common to other TKIs used in this condition and are those that clinicians are familiar with. Alopecia is relatively unusual with other TKIs in GIST but not usually significant providing patients are counselled about this in advance.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes this technology could be extrapolated to the UK population in terms of age and patient demographics and treatment setting. However it is likely in the UK population that a significantly smaller proportion of patients would have had more than 4 lines of treatment for GIST due to availability of drugs in the UK (a very small proportion of UK patients may have had more treatment lines if they had taken part in clinical trials for example) when compared to the INVICTUS study where 36% had 4-7 lines. One could argue that therefore the UK population may be a fitter one than that represented in the clinical trial. Most important outcomes are health related QoL, overall survival and progression free survival benefits weighed against toxicity of the drug. I am not aware of any other AE's that have been apparent following the reporting of INVICTUS nor have I come across any in clinical practice
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No- a number of UK patients have been treated with Ripretinib as part of expanded access programme but I don't think this data has been published yet
22. Are you aware of any new evidence for regorafenib since the publication of NICE technology appraisal guidance [TA488]?	https://pubmed.ncbi.nlm.nih.gov/31911828/- updated data on toxicity management in a real world setting, suggesting patients may benefit with improved side effect management/dosing https://pubmed.ncbi.nlm.nih.gov/28361439/ interesting cost effectiveness analysis of Regorafenib for GIST compared to Imatinib 4th line in Germany

23. How do data on real-world experience compare with the trial data?	I'm not aware of real world published experience for Ripretinib However in my own UK practice at RMH I have looked after a number of patients on expanded access Ripretinib in the 4th line setting who have had clinical benefit from the treatment and toxicity is manageable and in the expected range for TKIs
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	None that I can think of no- all patients should be eligible for this treatment within the inclusion criteria listed above

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	There is no data available to compare 4th line ripretinib against post progression regorafenib and this is very unlikely to ever be explored within the context of a randomised clinical trial - therefore we are highly unlikely to ever have this data in the future. The best comparison that we have available is against best supportive care. In clinical practice if ripretinib were available then GIST patients progressing on regorafenib would be switched to 4th line ripretinib
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	Although there is the usual caveat that patients that take part in clinical trials are generally fitter than those seen in the general population, 36% patients in the INVICTUS study had 4-7 lines of prior treatment whereas in the UK the vast majority will have had 3 lines only and by extrapolation may well be a fitter patient subgroup and perhaps more likely to respond with fewer resistance mutations. The INVICTUS trial included patients that were ECOG PS 1-2 which would fit with those patients with GIST in the UK that would be suitable for 4th line ripretinib.

Clinical expert statement

	In terms of age and other demographics these are largely similar to UK population
Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	This is a health economics question that I don't feel suitably well qualified to comment on.
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	In patients with GIST TKI's are usually used until evidence of clinical disease progression and this is in keeping with existing recommendations. When treatment is in the last line then if symptoms deteriorate significantly then TKI is stopped and patients are referred for best supportive care under the dedicated community palliative care team. In my experience patients with GIST on last line therapy do not continue treatment up to death. I do believe that clinicians would honour the stopping rules. It is important to note that disease progression in GIST is difficult to define and can be a nuanced decision. Radiologic response in GIST is notoriously difficult to determine and I note in the INVICTUS study Blind Independent Central Review (BICR) there was discordance of 20% between local investigator and BICR which emphasises the complexity and challenges in this area. In clinical practice an experienced clinician would use both radiologic changes in concert with assessment of patient clinical benefit to ascertain whether or not to continue drug
Uncertainty surrounding the level	Yes agree this is not well defined but would expect fairly rapid decline

of health-related quality of life experienced by patients after progression on fourth-line therapy	
Are there any important issues that have been missed in ERG report?	Not that I can think of

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Ripretinib represents an important advance in the management of advanced GIST, the first new treatment for over 5 years.

Ripretinib offers significantly improved progression free survival in patients while maintaining good quality of life.

Ripretinib has been shown to be effective in a range of GIST subtypes irrespective of primary mutation

Ripretinib is well tolerated and would be safely prescribed and managed within a designated network of GIST clinics

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with advanced gastrointestinal stromal tumours or caring for a patient with advanced gastrointestinal stromal tumours. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report, section 1.1, table 1.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **12 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with advanced gastrointestinal stromal tumours after 3 therapies

Table 1 About you, advanced gastrointestinal stromal tumours, current treatments and equality

1. Your name	Katy Jones-Cole
2. Are you (please tick all that apply)	☐ A patient with advanced gastrointestinal stromal tumours after 3 therapies? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced gastrointestinal stromal tumours? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	GIST Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with advanced gastrointestinal stromal tumours after 3 therapies? **If you are a carer (for someone with advanced gastrointestinal stromal tumours after 3 therapies) please share your experience of caring for them**	Diagnosed with metastatic gastrointestinal stromal tumours in August 2013 arising from the omentum/peritoneum (mutational status unknown due to spoiled biopsy), initially placed on Imatinib. Suffered severe side effects including tumour lysis syndrome and Cushing's Syndrome. Imatinib discontinued in September 2018 due to disease progression and started Sunitinib. Further disease progression, along with chronic diarrhoea so Sunitinib discontinued in January 2019. Enrolled on the Voyager Trial comparing Regorafinib with Avapritinib, randomised to Regorafinib, initially on full dose which was reduced to 120mg in May 2019 due to severity of side effects. Dose reduced to 80mg in July 2019 due to grade 3 Palmar-Plantar erythrodysesthesia, disease progression in September 2020. Prescribed Ripretinib in October 2020 on compassionate access programme via Prof Robin Jones at the Royal Marsden, Chelsea.
7a. What do you think of the current treatments and care available for advanced gastrointestinal stromal tumours after 3 therapies on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) From personal experience, I think Imatinib, Regorafinib and Ripretinib are 'wonder drugs 'as I had good results on all three. Sunitinib, however, almost wasn't worth taking as I had almost immediate disease progression and chronic diarrhoea. I suffered severe side effects with Imatinib, which resulted in periods of hospitalisation including a spell in ICU. b) I am a member of an online forum for people with GIST and their carers via GIST Cancer UK and my views appear to be similar to the majority.

8. If there are disadvantages for patients of current NHS treatments for advanced gastrointestinal stromal tumours after 3 therapies (for example, how ripretinib is given or taken, side effects of treatment, and any others) please describe these	Alopaecia - Hair loss commenced approximately 6 weeks after first taking Ripretinib, so after a further month, it had become so thin and patchy that I took the decision to shave my head. My hair has since grown extremely slowly, and is now very curly and 'frizzy'. I had always refused to let my GIST diagnosis define me, however since losing my hair, I am reminded of it every time I look in the mirror which has caused my mental health to dip as I feel my femininity has been compromised. Hand/Foot Syndrome (PPE) - I have very sore hands & feet, thickening of skin, callouses and skin peeling and therefore need to visit podiatrist (£33 per visit) on a monthly basis to have excess skin shaved off. I am unable to wear most shoes due to the soles of my feet being sore and can only wear those with memory foam soles such as Skechers. I soak my feet in warm water and Epsom Salts daily then apply Udderly Smooth Foot Cream. If I don't do this, my feet are sore to the point that I struggle to walk even a short distance without pain. SEVERE muscle cramps all over my body, mainly fingers and toes but occasionally in my neck, calves and back. This can happen at any time and is debilitating and extremely painful. The cramps tend to pass within 15-20 minutes although they often reoccur within a few minutes. I was initially prescribed quinine sulphate which helped enormously however this was stopped due to cardiac issues and I was recommended to take magnesium supplements however they make no difference. Cardiac - I get palpitations and when I am in bed trying to sleep, when I put my head on the pillow I can hear/feel my heartbeat. I wore a cardiac monitor for 14 days and was diagnosed with hypertension and ectopic heartbeats. As a result I take amlodipine 5mg which has successfully reduced my BP. Diarrhoea - I have bouts of diarrhoea at least twice a week, usually in the early hours of the morning, occasionally requiring the wearing of incontinence pants. I have tried changing my diet, keeping food diaries etc but to no avail.

9a. If there are advantages of ripretinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does ripretinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	a) Ripretinib has allowed me to continue with a good quality of life, as I have adapted to cope with the side effects. I took enforced medical retirement from my job as a clinical nurse specialist with the NHS in 2014 so I don't need to work, although I can care for myself with minimal assistance. I feel Ripretinib is better than regorafinib because the side effects are more manageable. I had to take regorafinib for three weeks then have a week off, and by week three the PPE & diarrhoea side effects were so severe I was able to do very little other than rest with my feet raised. b) N/A c) Ripretinib is my current treatment.
10. If there are disadvantages of ripretinib over current treatments on the NHS please describe these. For example, are there any risks with ripretinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The main side effects of Ripretinib that concern me are the cardiac issues and I worry that I will have a heart attack or stroke. I have had to call 111 in the past due to high blood pressure and palpitations and they sent me straight to A&E where I was monitored and then followed up with the 14 day cardiac monitor.
11. Are there any groups of patients who might benefit more from ripretinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I have mobility problems and I find it very easy to take ripretinib as it is in tablet form rather than having to attend multiple hospital appointments to have IV chemotherapy, so I would assume that other patients with reduced mobility would also benefit in this respect. Patients with dexterity impairment may find it difficult to undo the cap of the container although the other two treatments also come in similar containers.

12. Are there any potential equality issues that should be taken into account when considering advanced gastrointestinal stromal tumours after 3 therapies and ripretinib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I can't think of any potential equality issues.
13. Are there any other issues that you would like the committee to consider?	Ripretinib has 'bought' me at least an additional two years of life, for which I am eternally grateful.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	
Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	

Patient expert statement

Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy We consider patient perspectives may particularly help to address this issue. Please find more information about this issue in section 5.3.5 of the ERG report.	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I believe that Ripretinib has extended my life by at least two years.
- Whilst the side effects can be severe, they do not affect my quality of life - I have adapted my life accordingly.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in section 1.1, table 1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **12 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating advanced gastrointestinal stromal tumours after 3 therapies and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	Cambridge University hospitals NHS Foundation Trust
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced gastrointestinal stromal tumours? ☐ A specialist in the clinical evidence base for advanced gastrointestinal stromal tumours or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

8. What is the main aim of treatment for advanced gastrointestinal stromal tumours after 3 therapies? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aims are improve gist related symptoms, slow down or stop disease progression and possibly improve overall survival
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Stabilisation of tumour growth on CT scans Decrease in tumour size amounting to partial response Significant decrease in density on serial CT scans Improvement is gist related symptoms with better quality of life
10. In your view, is there an unmet need for patients and healthcare professionals in advanced gastrointestinal stromal tumours after 3 therapies?	At present, there is no standard of care and no licensed treatment available for patients with metastatic GIST who have had 3 lines of therapies. Not many patients for eligible for trials or cannot travel long distances to trial centres. There is a clear unmet need for a 4th line therapy for this group of patients.
11. How is advanced gastrointestinal stromal tumours after 3 therapies currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The current standard of care is—best supportive care, symptom control, hospice admission A small percentage of patients may be offered clinical trials in large centres but majority of patients may not be fit or cannot travel to larger centres. At present there are no clinical trials available in UK. From time to time we explore newer drugs within a compassionate/expanded access programme—these are available only for a short period. The pathway and management guidelines for GIST are well defined. British Sarcoma Group guidelines have been published in 2017 and are currently being updated. European guidelines have been published by ESMO. GIST patients are treated in specialist centres with clinicians who have expertise in managing the GIST and have experience with tyrosine kinase inhibitors. Ripretinib will have significant impact on the current pathway. It opens up another line of therapy for patients who otherwise will be treated as end of life. It

	helps to improve/control symptoms and slow down disease progression and hopefully, improve survival with good quality of life.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Ripretinib tablets will be used in the 4th line setting for metastatic/inoperable gist patients whose disease is progressing on 3rd line regorafenib. The technology will be used in designated specialist GIST/Sarcoma clinics with experienced healthcare professionals in this disease. No extra investments are needed, the clinics and the specialists are already well established in NHS. The technology is in oral form therefore, does require any further resources. Training can be provided by the specialist teams who have used this technology either in the trials or compassionate use programme. (online, webinar, educational sessions)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes—I strongly feel that the technology will provide meaningful symptomatic benefits compared with current standard of care. It is likely to improve the progression free survival with better symptomatic control. This is likely to result in a better quality of life compared with current standard of care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No—all patients groups with metastatic gist were included in the clinical trial. These groups include gist patients with KIT, PDGFRA, and wild type tumours.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	Very easy to implement within the existing clinic framework. No need for any extra resources. The specialist clinics are already in place in the centres where gist patients are currently treated.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The starting and stopping rules will be same as other treatments for GISTs. Routine blood tests, imaging at regular intervals, toxicity assessment. Starting rules—fit patient for 4th line therapy as assessed by specialist team, no significant comorbidities, progressed or intolerant to sunitinb/regorafenib. Stopping rules—On Ripretinib clinical disease progression with deterioration of general condition and performance status.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Ripretinib is well tolerated compared to the 2nd and 3rd line therapies for GIST. The improvements in progression free survival and overall survival are likely to translate in to a meaningful clinical benefit. The clinical trial used EORTC QoL measurements and this showed that the parameters remained stable on Ripretinib compared with placebo where there was decrease in QoL measurements.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The technology definitely qualifies as an unmet need in patients whose disease has progressed on 3rd line therapy. There is no standard of care after 3rd line regorafenib. It is innovative and is likely to help patients where no further treatments are available outside a clinical trial.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ripretinib side effects are generally mild to moderate and are manageable within the expertise in the context of specialist GIST/Sarcoma clinics. Both clinicians and specialist nurses are trained in managing side effects. Experience gained from other tyrosine kinase inhibitors is helpful.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes---this technology can be extrapolated to United Kingdom population. However, in UK we have access to 3 lines of therapy and it is very rare for patients to have 4th, 5th or 6th lines of therapy. In the clinical trial just over a third of the patients had 4 lines or beyond. This is not the scenario in UK. Most important outcomes are quality of life, progression free survival and overall survival. These benefits need to be balanced against the side effects of the drug. I am not aware of any other adverse effects which have been highlighted after the trial publication.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No-Ripretinib has been used in an expanded access programme in UK but the patient numbers are small and the data has not been published.
22. Are you aware of any new evidence for regorafenib since the publication of NICE technology appraisal guidance [TA488]?	German data on Regorafenib vs 4th line Imatinib https://pubmed.ncbi.nlm.nih.gov/28361439 Royal Marsden Regorafenib real life toxicity management https://pubmed.ncbi.nlm.nih.gov/31911828
23. How do data on real-world experience compare with the trial data?	No real world data on Ripretinib as yet.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any	I cannot think of any equalities issues with this technology

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	The best comparison is against best supportive care. There is no data available to compare Ripretinib in the 4th line against disease progression on regorafenib where regorafenib is continued beyond progression. It is highly unlikely that there will a randomised clinical trial in this setting to answer this question. In our clinical practice, if the patient's gist is progression on regorafenib, and they are fit to receive ripretinib then we will switch to Ripretinib.
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	In UK the gist population would have received 3 lines of therapy compared to the trial population where over a third of patients received 4-7lines of therapy. This is an unlikely scenario in UK. It is likely that the patients on 4th line Ripretinib are more likely to benefit compared to the trial population. The WHO/ECOG 1-2 is what we expect in UK practice

Clinical expert statement

Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	Post progression ripretinib use in the trial may have slowed the pace of disease progression-whether this has or hasn't influenced overall survival is difficult to ascertain.
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	Stopping rules for all TKIs are the same in all kinase driven cancers. If there is no further ongoing clinical benefit and the patient is deteriorating, then we discontinue the TKI and refer the patient for ongoing best supportive care. This will also apply to GIST patients on Ripretinib. However, assessing disease progression in GIST (in all lines of therapy) is not straight forward. Simple size measurements by RECIST may not reflect the true benefit. This is an area where specialist radiologist input would help. In real life, we use both ongoing clinical benefit (i.e patient symptomatically better, has improved quality of life and tolerating treatment well) and radiological response. Stable disease is an equally important end point. In GIST, like other kinase driven cancers, TKIs are discontinued when there is no ongoing benefit and TKIs are not continued right until the death of the patient.
Uncertainty surrounding the level of health-related quality of life experienced by patients after	Withdrawal of TKIs often results in rapid symptomatic deterioration and death. Agree that there is some uncertainty regarding the QOL assessment after progression on 4th line therapy,

progression on fourth-line therapy	
Are there any important issues that have been missed in ERG report?	None that I can think.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The timeline of introduction of systemic therapies in GIST stretches back to 2004. On an average there is a new line of therapy approved by NICE every 6-8 years. Last approved 3rd line Regorafenib was licensed in 2012. 10 years later we are exploring 4th line therapy. This is in contrast to other common cancers where there are multiple lines of therapies coming up every year.
There is desperate unmet need for a 4th line therapy in metastatic/inoperable GIST patients and Ripretinib fulfils that unmet need.
There is significant improvement in both progression free survival and overall survival.
Ripretinib is much better tolerated compared to the 2nd line and 3rd line therapies. Discontinuation due to toxicities is uncommon.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **12 September 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	[redacted] PAWS-GIST
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses **Regorafenib is currently the third and last licenced line of treatment for GIST cancer patients in England.** **For patients whose disease progresses on Regorafenib the alternatives are limited to; participating in a new clinical trial *(should a suitable one exist),* or continuing on Regorafenib until it no-longer has any control of tumour progression, at which stage it is stopped.** **Tumour progression happens because new mutations have developed beyond the control of Regorafenib.** **The opportunity to use Ripretinib, a drug specifically designed to target the newly developed mutations and prolong life is amazing.**
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses **The INVICTUS trial enrolled patients worldwide and in countries where there are a greater number of off-label therapies for GIST cancer than in England.**

		Any patient whose disease has progressed is urgently seeking a new therapy to continue their life. **In England patients are offered only three lines of therapy and this would seem to represent the majority of the patients in the INVICTUS trial.**
Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses **Difficult to comment from a patient perspective.**
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses **It is usual for patients to continue using TKI's while they are still gaining benefit as it is commonly understood that stopping use of a TKI will "take the brakes off" and disease will then progress far more rapidly.** **If a patient is no-longer benefitting from a TKI then it will be discontinued.**
Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses **Having engaged with a number of patients who have used Ripretinib the feedback was that they tolerated the drug much better than Regorafenib.**

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Sarcoma UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Absence of a comparison of fourth-line ripretinib against continued use of regorafenib post-progression	No	I am not aware of any data that compares these two treatments in this setting. Post-progression regorafenib is only used as it is the last line of treatment and clinicians looks to maximise benefit before a patient's sharp decline. Should ripretinib be introduced, there would be no post-progression regorafenib in this setting. Ripretinib should be compared to best supportive care.
Mismatch between the company's intended target population and the patient population enrolled in the INVICTUS trial	No	Whilst a third of the company's population in the INVICTUS trial had more than 3 lines of treatment, this is very unlikely to be the case within the NHS. The only patients in this setting who would have had more than the 3 approved lines of treatments currently available for routine use on the NHS would be the small number of patients who took part clinical trials for a new treatment or had access through an access programme. It is likely that patients on the NHS would be fitter and better able to tolerate this treatment than those who have had more than 3 lines.

		Further to this, the position of the ripretinib in the treatment pathway remains the same: a final life-extending option for those who would otherwise have only 4-6 weeks of life remaining.
Inappropriate assumption that post-progression ripretinib use in INVICTUS has not influenced overall survival outcomes and implausible overall survival predictions given the company's stopping rule	No	Unable to comment on this.
Proposed stopping rule is not in line with existing recommendations on the use of TKIs	No	This is a clinical question, but it is worth noting that similar trials have shown us that median PFS in this population on BSC is around 6 weeks, and that 'progression' in this setting is nuanced and should be carefully considered by the specialist MDT.
Uncertainty surrounding the level of health-related quality of life experienced by patients after progression on fourth-line therapy	Yes/No	Agree there is uncertainty.

Additional issues

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies.
Addendum: ERG comments on the company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Katy Cooper, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	22nd September 2022

1. Introduction

This addendum provides a summary and critique of the company's technical engagement (TE) response by the Evidence Review Group (ERG). Both the company's TE response and this addendum should be read alongside the company's submission[1] (CS) and the ERG report.[2]

The company's TE response consists of a written response document[3] and a revised version of the company's economic model. The company's TE response includes discussion around the five key issues raised in the ERG report,[2] as well as additional comments on a further issue relating to the company's assumptions around drug wastage. A summary of the key issues, the additional evidence presented in the company's TE response and the company's updates to their original model are summarised in Table 1. These issues are discussed in further detail in Section 2 of this addendum. Further economic analyses undertaken by the company and the ERG are presented in Section 3.

Table 1: Summary of key issues, additional evidence and updates to the company's model

Key issue discussed in ERG report[2]	ERG report section	Additional evidence presented in company's TE response[3]	Has the company's model been updated?
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])	• Further consideration of the feasibility of an ITC using data from studies of fourth- and subsequent-line regorafenib	No
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])	• Additional input from UK advisory board (August 2022) • Additional Kaplan-Meier plots for subgroups defined by number of prior therapies	No
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])	• Additional input from UK advisory board (August 2022)	No
Issue 4: Proposed stopping rule is not in line with existing recommendations on the use of TKIs	3.2	• Additional input from UK advisory board (August 2022)	No
Issue 5: Uncertainty surrounding the level of HRQoL experienced by patients after progression on fourth-line therapy	5.3.5 (critical appraisal point [6])	• Additional analysis of utility data for patients with progressed disease • Additional input from UK advisory board (August 2022)	Yes. Lower utility value applied in progressed disease state
Additional issue 6: Exclusion of drug wastage costs	N/a	• Additional input from UK advisory board (August 2022)	No

ERG - Evidence Review Group; OS - overall survival; TKI - tyrosine kinase inhibitor; HRQoL - health-related quality of life; N/a - not applicable; ITC –- indirect treatment comparison

2. Summary of company's response and ERG comments

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

The company's economic model includes best supportive care (BSC) as the sole comparator. However, the ERG's clinical advisors commented that in clinical practice, many patients (50% or more) who have progressed on regorafenib continue to receive regorafenib if they are still obtaining clinical benefit from it, unless their disease is progressing rapidly or they are experiencing significant toxicity, and if no further treatments are available. The ERG's clinical advisors commented that if ripretinib received a positive recommendation from the National Institute for Health and Care Excellence (NICE), they would switch patients onto fourth-line ripretinib as soon as they have progressed 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 company's TE response[3] on this issue can be summarised as follows:

- The company still considers that BSC is the only appropriate comparator for ripretinib.
- Previous appraisals of tyrosine kinase inhibitors (TKIs) used in the last line of therapy for gastrointestinal stromal tumours (GIST) (second-line sunitinib [TA179][4] and third-line regorafenib [TA488][5]) included BSC as the only comparator and were not compared against continued TKI therapy after progression on the previous line of therapy.
- An indirect treatment comparison (ITC) is unlikely to be feasible. The company explored studies which included regorafenib as fourth- or later-line therapy identified from the company's systematic literature review (SLR). Two studies were identified: Kang *et al.*[6] and Serrano *et al.*;[7] both of these studies included very few patients who received regorafenib at fourth-line or later (n=35 and n=14, respectively). Kang *et al.* report Kaplan-Meier plots for progression-free survival (PFS), but not overall survival (OS) and patient characteristics are presented only for the intention-to-treat (ITT) population rather than the fourth-line subgroup. Patients enrolled in the study reported by Serrano *et al.* alternated between sunitinib and regorafenib; hence, this study is not relevant. The company's TE response concludes that an ITC is unlikely to be feasible.

The ERG's view remains unchanged – regorafenib is currently continued after disease progression in a proportion of patients and a positive recommendation for ripretinib at fourth-line would likely result in a change in current practice. In principle, this indicates that continued regorafenib use after progression at third-line should be considered as a comparator for ripretinib. However, as noted in the ERG report,[2] it is unlikely that sufficient data exist to inform a reliable ITC. The ERG agrees that undertaking ITCs using Kang *et al.* and/or Serrano *et al.* would not resolve this uncertainty.

The ERG also agrees with the company that in both TA179 and TA488,[4, 5] BSC was considered as the only comparator. However, the ERG notes that both guidance documents also indicate that in clinical practice, sunitinib and regorafenib would continue to be given after disease progression in some patients:

- Sunitinib for GIST (TA179) - *"It [The Appraisal Committee] also heard from clinical specialists that, in practice, sunitinib could be given after disease progression because it was possible that some of the tumour might still respond to sunitinib. Also, many people might experience 'tumour flare' if sunitinib treatment was completely withdrawn."* (TA179 guidance,[4] Section 4.6, page 16).
- Regorafenib for GIST (TA488) - *"The clinical experts explained that treatment would only be stopped in clinical practice if there was clear disease progression and worsening clinical symptoms. Clinical guidelines recommend continued treatment with tyrosine kinase inhibitors as long as there is continued benefit… The committee concluded that using regorafenib after disease progression was in line with the marketing authorisation and current clinical practice."* (TA488 guidance,[5] Section 3.3, pages 8-9).

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

The company's intended positioning of ripretinib is as fourth-line therapy (in patients who have received exactly three prior therapies, including imatinib, sunitinib and regorafenib). In the INVICTUS trial,[8] 48 of 125 patients (37.1%) had already received at least four prior lines of treatment at study entry. The company's economic model is based on the ITT population of this trial. It is unclear whether the outcomes reported for the fourth- and later-line population in INVICTUS would be seen in the fourth-line population in NHS practice.

The company's TE response[3] makes the following points:

- The company held an advisory board meeting with UK clinical experts in August 2022. The experts stated that they *"expect patients treated with ripretinib to have outcomes which are the same or better in fourth line therapy compared to those reported in INVICTUS"*
- Subgroup analyses of PFS by number of prior lines of therapy in INVICTUS[8] (May 2019 data-cut) suggest a similar relative treatment effect for those with 3 prior lines of therapy and those with ≥4 prior lines (see Table 2).
- Subgroup analyses of OS by number of prior lines of therapy in INVICTUS (January 2021 data-cut) suggest a greater treatment effect for those with 3 prior lines versus those with ≥4 prior lines (see Table 2).
- The company's TE response also presents Kaplan-Meier plots for PFS and OS by subgroups with 3 and ≥4 prior lines of therapy, although these plots are not discussed in the text.

- The company's TE response concludes that *"by using the full INVICTUS population in the economic model, the company has made a conservative assumption with regards to efficacy of ripretinib in fourth-line GIST."*

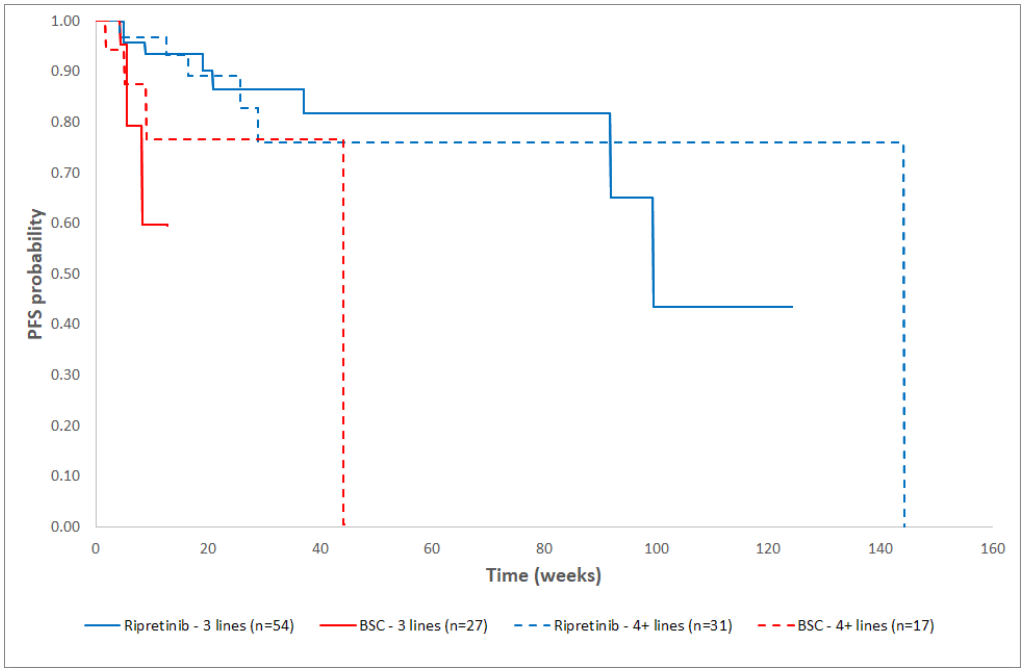
Table 2: Summary of subgroup results from INVICTUS by number of prior lines of therapy reported in the company's TE response

Endpoint	Data cut-off	HR (95% CI)	
		3 prior lines	≥4 prior lines
PFS	May 2019	[redacted]	[redacted]
OS	January 2021	[redacted]	[redacted]

HR - hazard ratio; CI - confidence interval; PFS - progression-free survival; OS - overall survival

The ERG's concerns around this issue related not only to whether the number of prior lines is a treatment effect modifier, but also whether it is a prognostic factor. This point is not explicitly discussed in the company's TE response.[3] The ERG notes that the Kaplan-Meier plots of OS by subgroup appear to exclude any adjustments for post-progression ripretinib use and are therefore difficult to interpret due to potential confounding. With respect to PFS, which is unaffected by open-label ripretinib use, the Kaplan-Meier plots do not clearly indicate better PFS for patients with 3 prior lines or ≥4 prior lines, nor do they clearly exclude this possibility (see Figure 1). However, the number of patients included in the subgroups is small, particularly in the placebo group, and the data are subject to high levels of censoring at later timepoints - this limits the extent to which any conclusions can be drawn. Overall, the ERG considers that it is possible that better outcomes may be seen if ripretinib is used exclusively at fourth-line, although this is uncertain, as is the impact on the cost-effectiveness of ripretinib.

Figure 1: PFS by prior therapy subgroup in INVICTUS – 3 prior lines versus ≥4 prior lines (data presented in Figures 4 and 5 of company's TE response digitised and overlaid by the ERG)



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

This issue concerns the company's proposed stopping rule for ripretinib and the uncertainty around the effect of continued open-label ripretinib after progression on OS in INVICTUS.[8] The company's base case analysis does not include adjustment of OS data from INVICTUS in the ripretinib group. The company's base case model predicts mean PFS and OS durations for the ripretinib group of [redacted] and [redacted] years, respectively (hence, mean time alive with progressed disease = [redacted] years). The ERG believes that the OS data from INVICTUS should be adjusted for post-progression ripretinib use in both treatment groups. The ERG's preferred analysis includes adjustment of these data using the simple two-stage method with re-censoring and results estimates of mean PFS and OS for the ripretinib group of [redacted] and [redacted] years. This shorter predicted OS duration increases the ICER for ripretinib compared with the company's base case analysis.

The company's TE response[3] states that: *"The company disagrees that ripretinib may result in additional survival benefit when used post-progression, since there is limited data to support this assumption."* In support of this position, the company makes the following points:

- UK clinicians who attended the company's advisory board in August 2022 were unable to predict the difference (if any) in survival in relation to the INVICTUS data[8] if treatment was stopped at progression.
- The ERG report[2] highlights uncertainty around the most appropriate method to adjust OS in the ripretinib arm, but prefers the simple two-stage method with re-censoring, in line with the CS.[1]
- The complex two-stage method, which includes all covariates that are likely to be prognostic of switching and survival (time to progression, Eastern Cooperative Oncology Group (ECOG) performance status, quality of life and age), could also be appropriate.
- Re-censoring has been used to protect against informative censoring, but this may lead to information loss. Analyses with and without re-censoring should be considered.

The company's TE response[3] concludes that *"Given the uncertainty regarding the most appropriate type of two-stage adjustment to perform, the unknown direction and magnitude of resulting biases, and the fact that UK clinicians were unable to predict the difference (if any) in survival in relation to INVICTUS data if treatment was stopped at progression, the company have not included any adjustment to the ripretinib arm to account for post-progression treatment."*

The concerns outlined in the ERG report[2] remain unchanged – the ERG believes that the company's assumption that post-progression ripretinib use has not influenced OS is inappropriate and that the presence of uncertainty around the magnitude of this effect is not a reasonable justification for excluding adjustment altogether. The ERG also highlights that the ERG's clinical advisors believed that open-

label ripretinib use will have influenced OS in INVICTUS[8] and that they did not consider the company's base case model (excluding OS adjustment in the ripretinib group) to provide plausible predictions of OS, given the company's stopping rule whereby ripretinib is given only until disease progression. The ERG also notes the following additional points:

- Adjustment of the OS data in the ripretinib group was included in CS Scenario Analysis 16 (see ERG report,[2] Table 29). However, as noted in Section 5.2.4 of the ERG report, the CS[1] and its appendices[9] do not provide any description of the methods used to adjust OS in the ripretinib group. Details of this statistical analysis were provided later as part of the company's response to response to clarification questions from the ERG (question B5).[10]
- The use of both the simple and complex two-stage models with re-censoring to adjust OS for open-label ripretinib use were discussed in the company's clarification response[10] (question B5). The company justified the selection of the simple two-stage model for the ripretinib group on the same basis as that for adjusting OS in the placebo group - because only the time to progression covariate was statistically significant and including other non-significant covariates would add further uncertainty into the analysis. Both the simple and complex two-stage models (including re-censoring) resulted in shorter durations of median OS for ripretinib compared to the unadjusted analysis. The estimated median OS from the complex model was longer than that obtained from the simple model (median OS for ripretinib group: ITT population (unadjusted) = 79.1 weeks; simple two-stage model with re-censoring = [redacted] weeks; complex two-stage model with re-censoring = [redacted] weeks). Mean estimates of OS were not presented.
- The company's executable model includes a drop-down menu which allows the user to select one of two options regarding the adjustment of OS in the ripretinib group: "No" (the company's base case) and "Yes" (simple two-stage method with re-censoring, as used in CS Scenario Analysis 16). However, the executable model does not include the functionality to apply the complex two-stage model for the ripretinib group, or to exclude re-censoring from either the simple or complex models, and the ICERs using these alternative adjustment models were not presented in the CS,[1] the clarification response[10] or the company's TE response.[3]
- The ERG considers that it may be informative to explore other scenarios using the simple and complex models, with and without re-censoring, as these alternative analyses have not been presented by the company. However, it is important that the model predictions of OS derived from survival models fitted to the adjusted data are clinically plausible.[11] Despite uncertainty around the magnitude of additional OS benefit resulting from open-label ripretinib given post-progression in the INVICTUS population, the ERG does not consider it plausible that patients with advanced GIST who have received at least 4 prior lines of therapy, who have progressed on ripretinib, and who then subsequently receive BSC alone, will survive for an average of [redacted] years.

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

The company's proposed stopping rule requires all patients to discontinue ripretinib upon disease progression. This is not consistent with current clinical guidelines on the use of TKIs for progressed GIST.[12, 13] 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.

The company's TE response[3] reiterates that a positive recommendation is being sought for ripretinib only up to the point of disease progression. The response states that the UK clinicians who attended the company's 2022 advisory board meeting stated that decisions about continuing treatment with ripretinib would take into account the patient's best interest and would be influenced by considerations of clinical benefit and tolerability. The experts commented that treatment would be stopped at clear progression. The company's response also comments that an exception may be made for heavily pre-treated GIST patients if radiological progression is limited, and the patient is tolerating therapy. The company suggests that this would apply to a minority of patients and would occur only if no other treatment options are available.

The ERG's concerns remain unchanged and the information provided in the TE response on how ripretinib would be used in practice is similar to that previously presented in the CS.[1] The ERG notes the following points:

- At the May 2019 cut-off of the INVICTUS trial,[8] nearly half (49%) of patients in the ripretinib group had moved on to receive 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, but may be higher. If the stopping rule was not applied, the proportion of patients who would be offered post-progression ripretinib in clinical practice is unknown. However, the ERG's clinical advisors stated that many patients continue to receive regorafenib after progression at third-line (one advisor suggested an estimate of 50%, whilst the other stated the *"vast majority"* would continue treatment).
- There are no other recommended treatment options for patients who have progressed on ripretinib.
- The ERG believes that may have been useful for the company to assess the cost-effectiveness of ripretinib excluding the proposed stopping rule. Such an analysis may not require adjustment of the OS data for the ripretinib group and could involve estimating treatment costs based on

the time to treatment discontinuation (TTD) data observed in the INVICTUS trial.[8] However, this analysis has not been presented.

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

This issue relates to the utility values applied in the company's model. The model applies health state utility values for the progression-free and progressed disease states of [redacted] and [redacted], respectively. These values are based on Euroqol 5-Dimensions 5-Level (EQ-5D-5L) data collected in INVICTUS[8] (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 in the company's original base case analysis is high and is very similar to that for the progression-free state (a difference of [redacted]), and that this is unlikely to be representative of the average level of HRQoL experienced by patients with advanced GIST who have progressed disease and are receiving BSC alone. The ERG's preferred analysis applies the utility value for patients with progressed disease derived from a published analysis of the GRID trial[14] (utility value = 0.647). This value was accepted by the Appraisal Committee in TA488[5] (third-line regorafenib).

The company's TE response[3] presents some discussion around the estimated utility value for the progression-free state and suggests that this is likely to be higher than expected due to the improved adverse event (AE) profile of ripretinib compared with other TKIs. However, the ERG's concern relates to the progressed disease state rather than the progression-free state. The company's TE response also includes a re-analysis of utility values for BSC patients with progressed disease excluding those who switched to receive ripretinib – a revised utility value of [redacted] has been included in the company's updated economic model. The company's TE response argues that this estimate *"better aligns to the modelled PD population."* The TE response also comments that UK clinicians who attended the company's 2022 advisory board meeting did not consider the data for regorafenib from the GRID trial to be comparable enough to ripretinib *"due to substantial difference[s] in tolerability."*

The ERG remains concerned about the company's updated EQ-5D analysis:

- The company's updated utility value for the progressed disease state of [redacted] appears to be based only on patients who were randomised to BSC who did not switch to ripretinib after progression. EQ-5D data from patients randomised to ripretinib who progressed but did not receive open-label ripretinib appear to have been excluded from the analysis. Consequently, the company's updated utility estimate includes only a small number of data points (company's original analysis: n=[redacted]; company's updated analysis n=[redacted]).
- Figure 2 illustrates the utility values applied in the company's original model,[1] the company's updated model[3] and the ERG's preferred analysis[2] (including age-adjustment applied by the

ERG). As shown in the plot, the company's updated utility value for the progressed disease state remains high and may lack face validity. As noted in the ERG report (Section 5.3.5, critical appraisal point 6, Table 32) previous EQ-5D estimates obtained from trials of earlier-line therapies for advanced GIST have reported comparatively lower utility values for patients with progressed disease (except for Zolic *et al.*,[15] which reports high utility values for patients with and without progression based on the GRID trial using the Swedish EQ-5D tariff).

- The ERG is unsure why the company's clinical advisors' concerns regarding differences in tolerability between regorafenib and ripretinib are relevant to determining the plausibility of the utility value for patients who have progressed and are receiving BSC alone. It is also unclear whether the company sought the views of the clinical experts regarding the plausibility of the updated utility value for the progressed disease state from INVICTUS – this is not mentioned in the company's TE response.
- Overall, the ERG remains uncertain regarding whether the utility value for progressed disease applied in the company's updated model reflects the average level of HRQoL experienced by patients with progressed disease receiving BSC alone over their remaining lifetime. As suggested in the ERG report,[2] further clinical input may be helpful in assessing the face validity of the utility values from the INVICTUS and GRID trials.

Figure 2: Age-adjusted utility values based on company's original model, company's updated analysis and ERG preferred analysis

Additional issue 6: Exclusion of drug wastage costs

The ERG report[2] noted that the company's original model did not include any costs associated with drug wastage – in other words, the model assumes that every tablet prescribed is taken. The ERG's preferred analysis assumes that all patients in the intervention group of the model incur a level of wastage which is equivalent to one quarter of a pack of ripretinib.

The company's TE response[3] states that the UK clinical experts who attended the company's 2022 advisory board meeting stated that there would be wastage for ripretinib. The experts noted that patients would be closely monitored and that the prescription and supply of ripretinib would closely match the patients' level of progression so that wastage would be tightly controlled. The clinicians estimated that any wastage would affect less than 5% of patients.

The ERG notes that whilst the company's clinical advisors commented that some wastage would be incurred, this has not been included in the company's updated economic base case analysis. The ERG is unsure what the company's clinicians meant when they stated that wastage would affect less than 5% of patients and the minutes of the advisor board meeting were not provided to the ERG. The ERG believes that, aside from any dose reductions or interruptions, some degree of wastage would be incurred by any patient taking an oral therapy if they stop treatment for any reason (e.g., due to intolerance, progression, or death) before completing a pack of treatment. The ERG retains its view that some level of wastage should be included in the model, but notes that this is not a key driver of the ICER.

3. Additional analyses presented by the company

The company has updated its base case analysis to include the utility value for progressed disease from BSC patients who did not switch to post-progression ripretinib in INVICTUS[8] (utility value = [redacted]), and includes age-adjustment of all utility values using Hernandez Alava *et al.*[16] The company's updated base case analysis also includes the ERG's error corrections detailed in Section 5.3.5 of the ERG report.[2] The company's updated model also retains the following features which were present in their original model:

- Ripretinib treatment is assumed to be discontinued at the point of progression (TTD = PFS).
- OS in the ripretinib group is not adjusted for open-label ripretinib use in INVICTUS[8]
- Costs associated with wastage are not included.

The results of the company's model are summarised in Table 3. The probabilistic version of the company's updated model suggests that the ICER for ripretinib versus BSC is expected to be £47,635

per QALY gained. The deterministic model suggests a slightly lower ICER of £47,280 per QALY gained. The company's TE response[3] also reports the results of one-way sensitivity analyses which suggest ICERs ranging from £32,547 to £80,995 per QALY gained; the key drivers of the ICER are the OS and PFS durations for the ripretinib group.

Table 3: Company's updated model results following technical engagement

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic model†							
Ripretinib	NR	[redacted]	[redacted]	NR	[redacted]	[redacted]	**£47,635**
BSC	NR	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,280**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*
† Results based on a re-run by the ERG. Note that the standard error for the updated utility value uses the standard error calculated using the overall progressed population in INVICTUS

The ERG does not believe that the company's updated results are appropriate for decision-making as they do not adjust for the impact of open-label ripretinib use on OS in INVICTUS.[8] Table 4 presents the results of the ERG's preferred analysis together with an additional scenario analysis in which the utility value for the progressed disease state is assumed to be [redacted]. As shown in the table, the inclusion of the updated utility value for the progressed disease state reduces the ICER from £134,241 to £130,100 per QALY gained.

Table 4: ERG additional scenario analysis – ERG preferred analysis including updated progressed disease utility value from INVICTUS, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis (EA5)							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£134,241**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis plus updated utility value for progressed disease state of [redacted]							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£130,100**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; EA - exploratory analysis
** Undiscounted*

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NICE National Institute for Health and Care Excellence

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

Additional information submitted by ScHARR: Plots of modelled overall survival curves including adjustment using simple, two-stage method with re-censoring in ripretinib and best supportive care treatment arms

1. **Modelled overall survival including simple, two-stage adjustment with re-censoring for ripretinib arm**

2. Modelled overall survival including simple, two-stage adjustment with re-censoring for best supportive care arm