Single Technology Appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more kinase inhibitors (review of TA881) [ID6496]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more kinase inhibitors (review of TA881) [ID6496]

Contents:

The following documents are made available to stakeholders:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 December 2025.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

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

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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 funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Overview	**Summary of comments from Deciphera** Deciphera would like to thank NICE for the opportunity to comment on the Draft Guidance (DG) for ripretinib. We welcome the committee's recognition of the substantial unmet need in adults with advanced gastrointestinal stromal tumours after 3 or more treatments (kinase inhibitors, including imatinib). However, we have material concerns that important evidence, expert opinion and uncaptured benefits have not been fully reflected in the current draft recommendations. Our comments focus on whether all relevant evidence has been taken into account, whether the summaries of clinical and cost effectiveness are reasonable, whether the provisional recommendations are suitable for NHS guidance, and any equality-related implications. **1. Has all of the relevant evidence been taken into account?** We consider that several key elements of the evidence base have not been appropriately reflected in the DG:

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	• **Survival modelling and re-censoring (Section 3.8):** The EAG's preferred two-stage OS adjustment with re-censoring removes substantial valid follow-up and leaves very few patients at risk at later timepoints. This is a recognised artefact in survival analysis and is explicitly cautioned against in NICE TSD24 when extrapolating long-term outcomes. In contrast, the company's analyses of OS without re-censoring allows for the retention of full follow-up, are methodologically simpler , and produce clinically plausible long-term OS consistent with independent expert clinical opinion (4–6% survival following 10 years of ripretinib therapy). The more mature OS data available in the 2022 DCO and TSE-IPCW analyses of OS in the 2021 DCO both indicate that the impact of informative bias is marginal. Therefore, the risks from potential informative bias in the two-stage estimation appear to be heavily outweighed by the loss of follow-up arising from re-censoring. • **Treatment pathway and prior/off-label therapies:** All INVICTUS enrolled patients received the three standard UK-licensed lines (imatinib, sunitinib, regorafenib), reflecting NHS practice prior to fourth-line therapy. Additional agents (e.g., pazopanib, sorafenib, nilotinib, avapritinib outside PDGFRA D842V, cabozantinib, investigational, and immunotherapy combinations) were used in only 1-10% of patients in the INVICTUS trial, and exclusively after standard lines. Nevertheless, these agents were used before ripretinib and there is no scientific evidence that they deliver durable survival in this setting, and their sporadic use is aligned with late-line access patterns in UK tertiary sarcoma centres. Similarly, we do not consider "off-label" exposure previous to ripretinib use or further supportive therapy a credible explanation for 10-year survivors, nor a reason to question the external validity of INVICTUS for the NHS. • **Clinical expert opinion and external evidence:** Clinical experts at the committee meeting clearly stated that a 10-year OS of 4–6% with ripretinib at fourth line and beyond is plausible. This aligns with the company's preferred extrapolation and is more conservative than the published survival data in earlier treatment lines. We do not believe this evidence has been adequately reflected in Section 3.9, nor in the choice of the most pessimistic extrapolation curve. • **Study size and strength of evidence:** INVICTUS is a randomised, controlled trial with a strength of recommendation of IA in the 2024 British Sarcoma Group GIST guidelines. This requires evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or a meta-analysis of well-conducted randomised trials without heterogeneity. It represents strong evidence of efficacy with a substantial clinical benefit, and means that ripretinib is strongly recommended. The INVICTUS sample size was calculated to show statistical differences between the ripretinib and placebo arm and is

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	comparable to trials previously accepted by NICE in similar rare oncology settings (for example, the GRID trial of regorafenib). We therefore believe that the DG underestimates the robustness and relevance of the trial evidence. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We do not fully agree that the DG provides a reasonable interpretation of clinical and cost-effectiveness evidence: • **OS extrapolation and "implausible" post-progression survival:** The committee has characterised the company's post-progression, off-treatment OS as implausible. Clinical experts, however, acknowledged the possibility of a real **legacy effect** of ripretinib and noted that the plausibility of some long-term survivors is clinically credible. The EAG's choice of with re-censoring and log-logistic extrapolation approach appears to prioritise the model fit across the initial estimates of the empirical hazard function and does not take into sufficient account the variable nature of this hazard. This prioritisation also appears to run counter to the long-term biological plausibility and expert opinion (contrary to the emphasis in NICE TSD14). • **Impact of off-label therapies on long-term OS:** The DG suggests that 10-year OS for patients having ripretinib in INVICTUS may have been materially influenced by off-label treatments unavailable in the NHS. Our detailed treatment history analysis shows that these exposures were rare, late-line and of uncertain benefit, and that the INVICTUS population closely mirrors UK practice (as supported by our 2024 advisory board, which unanimously agreed that INVICTUS is representative of UK clinical practice). It is therefore highly unlikely that such treatments materially drive 10-year OS or undermine the company's extrapolation. • **Uncaptured benefits in the economic model:** The DG states that there were no uncaptured benefits of ripretinib. This is inconsistent with the company submission and comments made at the committee meeting, which explicitly acknowledge: o The unmodelled **burden on carers and families**, including bereavement impact. o The **maintenance of health-related quality of life and functioning** on ripretinib, which is likely to reduce care needs. o The psychological **value of hope** and the ability for patients to experience additional life events, as highlighted by patient experts and supported by ISPOR guidance on including such elements in HTA, where feasible.

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	These factors are relevant when judging the most plausible ICER and should be recognised as uncaptured benefits rather than ignored. • **ICER threshold interpretation:** Given the rarity of the disease, (incidence of 1.5 out of every 100,000 people and approximately 900 to 1,000 new cases of GIST per year in the UK), the robustness of the RCT evidence and the uncaptured benefits, we question the decision to treat only ICERs at the [redacted] per QALY range as acceptable. NICE's own methods and process manual allows for greater flexibility and tolerance of uncertainty in rare diseases, particularly when evidence generation is inherently difficult. We feel that given the imminent increase in NICE's cost-effectiveness thresholds to £25,000-£35,000, some further flexibility should be afforded to this appraisal. **3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** In our view, the provisional recommendations are overly conservative and do not provide a fully sound basis for final guidance, for the following reasons: • The provisional recommendations give **more weight to a highly uncertain, with re-censoring** model than to without-re-censoring models that preserve more longer-term data, better reflect clinical opinion and are consistent with methodological guidance. • The provisional recommendations appear to **under-utilise expert clinician input** (including two ***lead UK*** clinicians that **were *independently chosen by NICE for the committee meeting, with over 20 years of experience in the*** management of GIST and with direct experience of ripretinib). This is contrary to NICE TSD14, TSD21 and section 6.2.7 of the NICE manual, which all stress the importance of clinical judgement in curve selection. According to the NICE manual, recommendations are developed using a range of evidence from literature searches and other sources, including real-world data and **expert testimony**. The manual also mentions that outcomes included in the evaluation are sometimes associated with uncertainty. As such, clinical expert opinion or expert elicitation is likely to be important. It stands to reason that, given the naturally higher uncertainty associated with a rare disease, this clinical input will be even more important. The provisional recommendations offer limited flexibility despite clear eligibility under Section 6.2.34 of the NICE manual (rare disease, strong RCT evidence, later-line, small population). • There is **additional evidence now provided, which further reduces uncertainty**, including the 2022 data cut and 4L-only KM curves (see addendum containing new analysis) intended to better reflect ripretinib's likely positioning in

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	clinical practice. These support both the clinical plausibility of long-term OS and the generalisability of the ITT population to UK practice. Taken together, these concerns suggest the draft recommendations may underestimate the true value of ripretinib and may not yet form a fair and balanced basis for final NHS guidance. **4. Equality, access and potential differential impact** Ripretinib is indicated for a **rare and advanced disease**, and there is a high medical unmet need for this patient population after they have exhausted the approved previous treatments. We do not identify specific adverse events for patients with specific characteristics relative to others *within* this group (for example, by sex, race or age). However, failure to recommend ripretinib may have **indirect equality implications**, including: • **Inequalities in access by geography and centre:** In the absence of NICE-recommended ripretinib, only patients treated at specialist centres with access to clinical trials or compassionate use programmes may be able to receive a similar therapy, potentially widening regional and socio-economic inequalities. • **Disproportionate impact on a rare, high-need group:** Adult patients with late-line GIST already face very limited options and poor prognosis after regorafenib. Restricting access to an additional active therapy has a direct impact on the prognosis and treatment options for this small population, contrary to NICE's stated aim of considering greater flexibility where evidence is hard to generate. • **Mental health and caregiver burden:** Denial of an additional line of therapy is likely to worsen distress and reduce hope for patients and families; this burden falls particularly heavily on those with an advanced, life-threatening disease. These impacts are not captured in QALYs but are important from an equality and fairness perspective. We believe the preliminary recommendations may therefore **insufficiently account for the needs of a rare, high-burden population** and the broader psychosocial consequences of not providing a fourth-line option. Recognising these issues would support a more flexible and equitable interpretation of the evidence and a greater acceptance of residual uncertainty in this appraisal.
1	**Re-censoring data and fit to empirical hazard (Draft Guidance Section 3.8)** *"The EAG noted that none of the extrapolated models that were fitted without re-censoring provided a satisfactory fit to capture the timing of the first hazard increase in the 2-stage adjusted data"* *"It [the committee] concluded that the EAG's preferred approach, which included re-censoring within the 2-stage adjusted complex model and extrapolated using the log-*

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	logistic model, was more aligned with the empirical hazard and so was the most appropriate analysis." **Comment from Deciphera** *EAG and committee preference for re-censoring* The EAG and committee's preferred approach incorporates the use of the two-stage adjustment with re-censoring of the IPD. The use of re-censoring substantially reduces the number of patients contributing information at later time points, limiting the ability of survival extrapolations fitted to that data to capture important changes in the hazard in the longer term. This approach is also somewhat contradictory to the committee's comment about the small number of people taking part in INVICTUS (Draft Guidance Section 3.10), in that it further reduces the study sample size and potentially further increases uncertainty in the extrapolations derived from the reduced sample size The company notes that the committee appears to have favoured the with-censoring analysis based on how closely the resulting extrapolations fitted the modelled empirical hazard. We would argue that this does not represent a logical approach to determining whether the analyses of OS with re-censoring are more reliable than those without. The primary consideration should be whether the uncertainty introduced by the considerable loss of information arising from re-censoring the data is outweighed by its potential to address informative bias from the two-stage estimation procedure. *Loss of information from re-censoring* During the two-stage estimation analysis for patients randomised to ripretinib, a total of [redacted] patients have their event time transformed. However, when the analysis is performed using the complex generalised gamma model with re-censoring, the last event in the transformed data occurs when [redacted] are at risk, whilst all other patients have been censored or died before this time. This results in the previously estimated survival probability of [redacted] dropping by approximately half to [redacted]. As such, it is highly doubtful that this drop reflects a true sudden increase in the risk of death. Furthermore, when re-censoring is applied to the 2021 data cut, there is no data beyond 45 weeks, a time point which precedes a plateauing of the Kaplan-Meier curve in the longer term. As such, extrapolations fitted to this data do not reflect this phenomenon and would likely underestimate survival for patients having ripretinib. The uncertainty introduced by using the with re-censoring analysis is reflected in the comparison of the modelled versus empirical smoothed hazard functions, in which there is a considerably wider variability between the modelled hazard functions with re-censoring (Figure 2) compared with the analysis without re-censoring (Figure 1). Note that the smoothed empirical hazard in these plots have been estimated using a natural cubic spline with a 95% confidence interval to show the uncertainty of the smoothed hazard.

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	Figure 1: Empirical and modelled hazard functions based on the 2-stage estimation BID-adjustment (complex, generalised gamma) without re-censoring  *Figure 2: Empirical and modelled hazard functions based on the 2-stage estimation BID-adjustment (complex, generalised gamma) with re-censoring*  NICE DSU Technical Support Document 24 (TSD24) acknowledges the issues related to applying re-censoring, noting the loss of longer-term data and that "The loss of follow up information and the early truncation of the survival curves, due to re-censoring, may have an impact in terms of increased uncertainty when the intention is to extrapolate survival beyond the period of the trial". TSD24 also states that "this is likely to be the case when important changes in hazards occur beyond the re-censored follow-up times, and/or when important changes in the treatment effect occur beyond the re-censored follow-up times". As noted above, we consider this to be the case here.

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	Informative bias introduced by two-stage estimation NICE TSD24 notes that two-stage estimation can induce informative censoring because censoring and survival times are only adjusted for patients who switch. Patients who switch are likely to have a different prognosis compared to those who do not switch. Treatment switching is often associated with prognostic characteristics, creating a relationship between prognosis and censoring times and leading to informative censoring. The purpose of re-censoring, as described in TSD24, is to break this dependence by estimating adjusted potential censoring times for all patients in a treatment arm in which switching occurs, not only those who switch. Applying re-censoring results in a lower number of patients still at risk (after re-censoring), in combination with the arbitrary timing of the administrative censoring cutoff date, all contribute to the loss of longer-term follow-up in the re-censored analysis. Whilst re-censoring may reduce bias in one direction, in INVICTUS it introduces substantially greater uncertainty by discarding information in the form of survival time. *Conclusion on appropriateness of not re-censoring* In conclusion, we consider that in a scenario where the aim is to extrapolate in the long term far beyond the period of the clinical trial, the loss of information from re-censoring introduces more uncertainty than its potential to address any informative bias within the two-stage estimation procedure. We consider this to be the case for both the 2021 and 2022 data cut-offs. [redacted] the loss of information from re-censoring is still evident (see addendum containing new analysis) Our preferred approach, without re-censoring, retains more follow-up information and is supported under NICE's technical guidance. The OS extrapolation with re-censoring was deemed clinically plausible and consistent with clinician feedback during the committee meeting, estimating a 10-year OS of between 4-6%. *Two stage estimation with inverse probability of censoring weighting (TSE IPCW)* However, to resolve some of the uncertainty on this point, we have introduced a new TSE-IPCW approach as part of our updated analyses (*Figure 3*). The purpose of this additional method is to better account for the non-random nature of dose escalation in INVICTUS. Specifically, TSE-IPCW enables us to adjust survival times for observed prognostic differences between switchers and non-switchers using a standard TSE approach, thereby removing informative censoring without requiring re-censoring of survival times[1]. This approach has been externally validated by a lead biostatistician, who is involved in co-authoring both TSD16 and 24, as well as multiple publications on treatment switching. We consider that TSE-IPCW provides an important complementary perspective that helps characterise uncertainty surrounding the potential impact arising from informative censoring within the TSE analysis. However, due to the novel nature of this approach and, to our knowledge, its lack of precedent within NICE appraisals, our preferred base case remains the analysis without re-censoring. Further information as to this approach is provided

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Figure 3: Kaplan−Meier plot of time since randomisation to death, subjects randomised to Ripretinib 150mg OD (N=85).

Impact of re−censoring of counterfactual (CF) survival times within two−stage estimation (TSE) adjustment and TSE with Inverse Probability of Censoring Weighting (IPCW) of IPDE. CF survival estimated via the Complex, Generalised Gamma parametric survival model. (DCO: 2021)

Fitting smoothed hazards to empirical hazards

NICE DSU Technical Support Document 14 (TSD14) emphasises that extrapolation should prioritise clinical plausibility and stability of long-term predictions, rather than overfitting to short-term noise in sparse hazard estimates. The risk of placing too much emphasis on fit to the empirical hazard is emphasised by the newly generated smoothed empirical hazard functions (Figure 4-5), derived using [redacted]. The smoothed hazard for the TSE without re-censoring, in particular, differs in shape from that originally calculated and is more closely aligned with the extrapolation models. The 95% confidence interval also shows the uncertainty of the true shape of the smoothed hazard.

Furthermore, when considering the timing of the first empirical hazard increase, an earlier increase in the risk of death, as represented in the extrapolation models, compared with the empirical hazard, implies a conservative approach. This is because patients will die earlier in the model time horizon, at a point where reduced discounting means that the resultant loss of QALYs will be more impactful.

As described above, the models without re-censoring produce long-term OS estimates at approximately 4–6% at 10 years, which closely align with clinical expert opinion. In contrast, re-censoring removes observed follow-up, resulting in a loss of [redacted] and imposes additional structural assumptions to match an early hazard feature of questionable robustness. Also, the 1.89% 10-year OS, which is suggested by the EAG, is significantly lower than the clinical experts' opinion heard during the committee meeting (4-6%) and the company's values for 10-year OS extrapolation.

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	Therefore, although we acknowledge that the survival extrapolations in the analysis without-re-censoring do not have as close a visual fit to the empirical hazard as the with re-censoring analysis, they provide a more robust and clinically credible basis for projecting long-term overall survival, aligned with expert guidance and grounded in the full observed data rather than relying solely on early outcomes or assumptions about long-term survival. We have generated models fitted to the 2022 DCO, which show that the extrapolated models fitted without re-censoring provide a satisfactory fit to the two-stage adjusted data (Figures 4-5). *Figure 4: 2022 data cut Hazard functions of observed and parametric functions for Overall Survival (Weeks) − QD to BID Crossover (Two−stage model with IPCW: Complex, Generalised Gamma, patients randomised to Ripretinib only)* 

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	Figure 5: 2022 data cut Hazard functions of observed and parametric functions for Overall Survival − QD to BID Crossover (Two−stage Model: Complex, Generalised gamma, With re−censoring, patients randomised to Ripretinib only)  References 1. Latimer NR, Abrams KR, Siebert U. Two-stage estimation to adjust for treatment switching in randomised trials: a simulation study investigating the use of inverse probability weighting instead of re-censoring. *BMC Med Res Methodol.* 2019;19:69
2	**Plausibility of OS predictions generated by the economic model (Draft Guidance Section 3.9)** *"The clinical experts at the meeting explained that in recent years, treatment options earlier in the pathway have changed and now include more surgery, precision medicine and better management of side effects. Because of this, survival estimates are now better (around 4-6%). "* **Comment from Deciphera** The company does not believe that this part of the guidance accurately reflects the conversation that occurred during the meeting. When asked for 10-year OS estimates, the two clinical experts independently chosen by NICE stated that 4-6% OS with ripretinib was realistic, but did not attribute this survival to more surgery, precision medicine and better management of side effects, but instead to ripretinib, saying that 4-6% OS after 10 years with ripretinib was plausible. In general, we feel section 3.9 is somewhat unclear and not reflective of how the conversation occurred in the meeting, and propose that below is an accurate reflection of the conversation during the committee meeting (content in bold updated): **"The company had sought expert clinical opinion on the plausibility and validity of the survival probability produced by the OS modelling it used in its economic model. Published evidence indicates that 10-year survival following first- and second-line GIST therapy ranges from 10% to 23%, declining to approximately 10%**

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	for patients who have received second-line sunitinib. After progressing on regorafenib, prognosis is poor, with clinical advisers estimating from the company advisory board in 2024 that 10-year survival for patients who have received ripretinib in 4L to be between [redacted]. These data are consistent with the company's model projections. The consensus opinion of the clinical advisers was considered confidential by the company and therefore cannot be presented here. Clinical experts during the committee meeting, when asked about 10-year OS, stated that 4-6% OS after 10 years when treated with ripretinib at fourth line onwards was plausible. This was in line with the projection from the company's base case extrapolation. The clinical experts' estimates considered recent advances in the management of advanced GIST, including more surgery, precision medicine and better management of side effects. The EAG considered that its alternative modelling approach (using re-censoring and log-logistic extrapolation) produced better external validity. This was because its extrapolation projected a 10-year survival that was closer to the consensus opinion of the clinical advisers consulted by the company. The committee noted that using the company's approach seemed to yield implausible OS estimates in the ripretinib arm in the post-progression, off-treatment state. The clinical expert responded that because patients in INVICTUS were having treatment abroad, they may have had off-label treatment with other drugs, such as immunotherapies, or participated in **clinical trials. So, this may have had a stabilising effect.** The EAG stated that their clinical advisers had said they would expect no residual effect after stopping treatment, and the EAG's preferred analysis (using re-censoring) showed less modelled survival gain after progression compared with the company's modelled survival (without re-censoring). The committee recognised that patients in current clinical practice who have treatment at this point in the pathway may be different to the patients in the trial. However, the OS estimates in the economic model were based on the population in INVICTUS, where patients had exhausted all other options and had progressed after receiving regorafenib. **It highlighted that the decision modifier (and other model inputs) is based on the INVICTUS population, a proportion of INVICTUS' patient papulation was heavily pretreated (with more than 3 previous treatments) compared to the patient population expected to be treated in current clinical practice.** The committee acknowledged the uncertainty generated through different clinical expectations of survival as the treatment pathway improves. The committee concluded it preferred to consider the INVICTUS trial data when extrapolating OS to 10 years in the economic model."**
3	**Implausible OS estimate in the ripretinib arm post progression off treatment (Draft Guidance Section 3.9)** *"The committee noted that using the company's approach seemed to give implausible OS estimates in the ripretinib arm in the post-progression, off-treatment state"* **Comment from Deciphera** We acknowledge the EAG's observation that the company's approach to predicting OS in the model appeared to yield implausible OS estimates in the ripretinib arm during the post-progression, off-treatment state. However, clinical experts at the committee meeting explained that it is possible that there could be a "legacy effect" of ripretinib, in which the ongoing benefit of ripretinib persists after a patient has discontinued treatment. In addition

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<table>
<tr><td></td><td>to the potential legacy effect, there is the potential that the "implausible" post-progression, off-treatment OS estimates are a by-product of the partitioned survival modelling approach, in which independent extrapolation models of treatment discontinuation and OS are applied in the long term beyond the trial period.</td></tr>
<tr><td>4</td><td>Patients in INVICTUS receiving off-label treatments influencing 10-year OS (Draft Guidance Section 3.9)

“The committee noted that using the company's approach seemed to give implausible OS estimates in the ripretinib arm in the post-progression, off-treatment state. The clinical expert responded that because patients in INVICTUS were having treatment abroad, they may have had off-label treatment with other drugs, such as immunotherapies. So, this may have had a stabilising effect."

Comment from Deciphera
Expert comments suggested that the 10-year OS estimate of approximately 4-6% may have been influenced by off-label therapies not available on the NHS. However, a detailed review of prior treatments in INVICTUS (a multinational trial with UK sites) and their relevance to UK practice suggests that this explanation is unlikely.

All patients in the trial had received the three standard UK-licensed treatments for advanced GIST (imatinib, sunitinib, and regorafenib), reflecting the NHS sequence prior to fourth-line therapy. This suggests that the study population is highly representative of UK clinical practice. In both arms, all patients had progressed through these treatments.

Although several additional agents reported in the trial are not licensed for GIST in the UK, [redacted], these were used in very small proportions of the study population, typically [redacted] each (Table 1), and only after exhaustion of the three standard lines, but before ripretinib.

Table 1: Percentage of patients receiving prior therapies in INVICTUS and timing relative to ripretinib
<table>
<tr><th>Treatment</th><th>% of Patients (Total N=129)</th><th>Timing vs Ripretinib</th></tr>
<tr><td>Imatinib</td><td>129 (100%)</td><td>Before</td></tr>
<tr><td>Sunitinib</td><td>129 (100%)</td><td>Before</td></tr>
<tr><td>Regorafenib</td><td>129 (100%)</td><td>Before</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Avapritinib (outside PDGFRA D842V)</td><td>6 (4.7%)</td><td>Before</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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	This pattern mirrors real-world UK practice, where patients treated at tertiary sarcoma centres may access compassionate-use programmes, clinical trials, or experimental therapies once standard options are depleted. Crucially, we do not believe that these low-frequency, late-line exposures are sufficient in prevalence or expected efficacy to generate a meaningful shift in long-term survival outcomes. There is no data available from INVICTUS regarding subsequent therapy; however, there are no other treatments currently indicated as ≥4L treatment options in this patient population. The agents used off-label in the INVICTUS trial have minimal evidence of producing durable long-term survival in heavily pre-treated patients with GIST. Apart from imatinib, sunitinib, regorafenib, and ripretinib, all other prior therapies recorded in the trial are off-label for GIST in the US, UK and Europe. Their usage reflects late-line trial activity and compassionate access that occurs similarly in major centres internationally, including the UK. None of the off-label prior treatments is associated with sustained disease suppression beyond a few months in the advanced GIST setting, and none has demonstrated survival benefits approaching those required to materially elevate 10-year OS. It is therefore implausible that such drugs could account for long-term survivors observed in the model. [redacted] To summarise, although a small proportion of trial participants received off-label therapies, these agents were used infrequently, lack evidence of long-term survival benefits, and were introduced only after standard UK-relevant therapies had failed but before patients had ripretinib. The trial population, therefore, remains highly generalisable to NHS practice, and the presence of 10-year survivors cannot reasonably be attributed to access to off-label treatments unavailable in the UK. Therefore, the 4-6% 10-year OS estimate which was supported by clinicians in the committee meeting is plausible and

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	does not appear to be influenced by use of off label treatments in the INVICTUS trial population. References [redacted]
5	**Impact of clinical expert opinion on survival curve selection (Draft Guidance Section 3.9)** *"The committee acknowledged the uncertainty generated through different clinical expectations of survival as the treatment pathway improves. The committee concluded it preferred to consider the INVICTUS trial data when extrapolating OS to 10 years in the economic model"* **Comment from Deciphera** We do not believe that the committee has adequately considered the clinical expert input when selecting the most appropriate survival curve for ripretinib. The committee appears to have largely disregarded the views of the experts who participated in the meeting and has selected a curve that is more pessimistic than even the advisory board consensus. Historically, clinician estimates of survival for patients with advanced GIST treated for the assessment of TKIs have been conservative. Long-term survival for imatinib was severely underestimated at HTA as recent observational studies now show PFS rates of nearly 10% at 10 years for first-line patients with advanced GIST treated with imatinib.[1] In contrast, during NICE's appraisal of imatinib [TA86], the Committee concluded that the

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	cost-effectiveness estimates based on a 10-year time horizon were sufficient to encompass the key costs and benefits – suggesting that there would be no patients remaining alive at this timepoint.[2] During the sunitinib technology assessment [TA179] clinical experts estimated 10% survival at 6 years.[3] However, a recent study has shown that median OS for second line treatment with sunitinib is 63.4 months (i.e. 50% of patients alive at 5.3 years) with ~10% of patients surviving to 10 years.[4] These factors mean that raw trial survival figures may systematically underestimate real-world outcomes in late-line GIST; given this, values towards the upper end of the expert-elicited range are likely to be more appropriate. NICE TSD14, TSD21 and section 6.2.7 of the NICE manual all emphasise the importance of incorporating clinical expert opinion into survival curve selection. In this appraisal, the two clinical experts providing input each have more than 20 years' experience treating GIST, and both have direct clinical experience using ripretinib. There is therefore no clear basis for discounting their opinions, particularly when they provide context that cannot be derived from the trial data alone. In addition, we are concerned that the committee and EAG appear to have placed limited or no weight on the broader evidence submitted regarding survival outcomes on earlier-line treatments. This evidence supports the view that survival under current treatment pathways is improving, and that the conservative assumption adopted by the EAG and committee risks underestimating long-term survival for patients receiving ripretinib in UK clinical practice. <u>References</u> 1. Casali PG, Zalcberg J, Le Cesne A, et al. Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels. Journal of Clinical Oncology. 2017;35(15)doi:10.1200/JCO.2016.71.0228 2. National Institute for Health and Care Excellence. Appraisal Consultation Document: Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours [TA86] Accessed 05/12/2024, https://www.nice.org.uk/guidance/ta86/documents/appraisal-consultation-document-imatinib-for-the-treatment-of-unresectable-andor-metastatic-gastrointestinal-stromal-tumours 3. National Institute of Health and Care Excellence. Sunitinib for the treatment of gastrointestinal stromal tumours [TA179]. Accessed 24/05/2024, https://www.nice.org.uk/guidance/ta179/resources/sunitinib-for-the-treatment-of-gastrointestinal-stromal-tumours-pdf-82598444073925 4. Mohammadi M, Jansen-Werkhoven TM, Ijzerman NS, et al. Dutch Gastrointestinal Stromal Tumor (GIST) Registry Data Comparing Sunitinib with

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	Imatinib Dose Escalation in Second-Line Advanced Non-KIT Exon 9 Mutated GIST Patients. Target Oncol. Nov 2022;17(6):627-634. doi:10.1007/s11523-022-00926-6
6	**EAG and committee request for 2022 INVICTUS data cut (Draft Guidance Section 3.10)** *"The EAG noted that the 2022 data could provide additional information to inform long-term OS predictions and provide more reliable estimates. It considered longer-term data would help to reduce the impact of information loss caused by re-censoring"* *"It [the committee] concluded that for its decision making it would find additional data from the May 2022 data cut of INVICTUS helpful or sufficient justification from the company explaining why the data was assessed as poor quality. The committee noted it would be useful if additional data included information on the numbers of people with disease progression in INVICTUS"* **Comment from Deciphera** In line with the committee's request and to further resolve uncertainty, we have provided the additional data from the May 2022 data cut from INVICTUS (see addendum containing new analysis). This includes the same 2-stage estimation BID adjustment analyses as was provided for the 2021 data cut. Information on the numbers of patients with disease progression in INVICTUS has also been provided below (Table 2). Cost-effectiveness scenario analyses using the 2022 data cut to inform OS have also been provided (see addendum containing new analysis). However, in line with our position at the first committee meeting, our preference remains to use the January 2021 data cut for the following reasons: • The 2021 DCO was prespecified, complete, and already includes mature OS, PFS, and HRQoL data, ensuring robustness of the base case, in addition to aligning with clinical expectations. [redacted] • The TSE analysis of the OS data from the 2022 data cut necessitates the use of progression data from the 2021 data cut. There is the high potential to introduce bias given this disparity in data sources for the calculation of post-progression survival. It is not inconceivable that this bias might easily out-weigh other sources of bias, such as informative censoring. The 2021 data cut produces extrapolations more in line with the clinical expert feedback.

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[redacted]

Unlike the prespecified 2021 DCO, the 2022 cut only included OS and safety. PFS and HRQoL were not recorded subsequent to the 2021 DCO, such that re-running the model using a partial mix of 2021 and 2022 data will create additional temporal heterogeneity across clinical and patient-relevant outcomes (PFS, TTD, OS, HRQoL).

Table 2: Summary of progressions pre- / post-2021 DCO in the ITT subjects (N=129)
<table>
<tr><th>Outcome</th><th>Ripretinib 150 mg QD n / N (%)</th><th>Placebo n / N (%)</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>7</td><td>Consideration of the challenges of producing robust evidence and appropriate flexibility (Draft Guidance Section 3.10)

“The committee recognised the challenges of producing robust evidence in a small population. It noted that a bigger trial could have compared people who had the increased dose with those who did not. But it noted that this would have taken time and been expensive to carry out”

“The committee considered the extent of OS benefit was very uncertain. This was because of the small number of people taking part in the trial”</td></tr>
</table>

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	Comment from Deciphera We do not believe that sufficient consideration has been given to the quantity or quality of evidence presented in the committee meeting. Although it is stated that "The committee recognised the challenges of producing robust evidence in a small population", we do not believe that sufficient flexibility has been applied in this appraisal, especially where the trial is concerned. In the British Sarcoma Group clinical practice guidelines for GIST, the strength of the recommendation for ripretinib is [IA], meaning:[1] • Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for a bias) or meta-analyses of well-conducted randomised trials without heterogeneity; • Strong evidence for efficacy with a substantial clinical benefit, strongly recommended. The INVICTUS sample size was calculated to demonstrate statistical differences between both arms and is comparable to that of studies in other rare diseases. For instance, the GRID study, which assessed the efficacy of regorafenib for advanced GIST after failure of imatinib and sunitinib, included 199 patients in its efficacy analysis. In its appraisal of regorafenib, the NICE committee did not express concerns about the study's size.[2] Since ripretinib is indicated for a later line of therapy, it is expected that the INVICTUS trial would have a smaller sample size than GRID, reflecting the smaller available patient population to recruit from. Given this, we would request that such statements around the INVICTUS sample size are qualified and quantified in some way; for example, by noting that they are made in comparison to treatments for more prevalent indications. <u>References</u> 1. Judson I, Jones RL, Wong N, et al. Gastrointestinal stromal tumour (GIST): British Sarcoma Group clinical practice guidelines. British Journal of Cancer. 2024;7(6)doi:https://doi.org/10.1038/s41416-024-02672-0 2. https://www.nice.org.uk/guidance/ta488/resources/regorafenib-for-previously-treated-unresectable-or-metastatic-gastrointestinal-stromal-tumours-pdf-82605033207493
8	**Uncertainty around the line of therapy in which ripretinib would be given in UK clinical practice (Draft Guidance Section 3.12)** *"In INVICTUS people may have had treatment beyond progression before a fourth-line treatment, but if ripretinib was routinely available in clinical practice some people may switch to a fourth-line treatment immediately after progression….* *So generalisability to the population that would have ripretinib in NHS clinical practice is uncertain."* **Comment from Deciphera** The company accepts that clinicians have expressed the opinion that if ripretinib was routinely available in NHS clinical practice, patients would likely switch to it as a fourth-

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	line option immediately after progression on regorafenib. ESMO guidelines state that ripretinib at the dose of 150 mg daily is the standard fourth-line treatment in patients progressing on or intolerant to imatinib, sunitinib, regorafenib [I, A; ESMO-MCBS v1.1 score: 3][1]. We consider that it remains preferable to use data from the INVICTUS intention to treat (ITT) population for the base case analysis, despite the fact that some of these patients received more than 3 prior lines of therapy. This is to align with NICE's preference for use of the ITT population to support internal trial validity, and also to maximise the available sample size. To reflect how ripretinib is most likely to be positioned in routine clinical practice, additional subgroup analyses have been carried out for patients who entered INVICTUS after exactly 3 prior therapies (true fourth line). Both the adjusted and unadjusted KM curves show better OS compared with placebo and broadly similar PFS compared with patients receiving ripretinib after 4 or more prior lines (see addendum containing new analysis). [redacted] References 1. Gastrointestinal stromal tumours: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up, https://www.sciencedirect.com/science/article/pii/S092375342104480X 2. Deciphera Pharmaceuticals L. Data on File. Ripretinib NICE re-submission advisory board meeting: Friday, 26th July 2024. 2024. 3. Deciphera Pharmaceuticals L. Data on File. Ripretinib NICE evaluation Advisory board meeting: Tuesday, 30th August 2022. 2022.
9	**Mutational testing in GIST (Draft Guidance Section 3.12)** *"Regorafenib may not be given if testing has suggested that there is a mutation that means it will not be effective"* **Comment from Deciphera** Genetic testing is not routinely conducted in clinical practice in England and Wales for patients with GIST, either at the point of diagnosis or disease progression. As such, this comment is inaccurate and should be removed.
10	**Acceptable ICER (Draft Guidance Section 3.13)** *"The committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)"*

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	Comment from Deciphera Section 6.2.33 of NICE's health technology evaluations manual states that "the committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult because they are: • rare diseases • for use in a population that is predominantly children (under 18 years old) • innovative and complex technologies. In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition or technology(s) affects the ability to generate high-quality evidence before applying greater flexibility." Soft tissue sarcoma accounts for 1% of malignancies in adults, and GIST accounts for approximately 7% of those cases (GIST incidence = 1.5 out of every 100,000 people).[1,2] Advanced GIST in the fourth-line setting is therefore certainly a rare disease and so would qualify for special consideration under this section of the manual. However, we do not feel that the committee has truly considered the rarity of this condition and the opportunity that ripretinib can provide for these patients with later-line disease, as was outlined by the patient expert in the committee meeting. We therefore believe that there is scope within this appraisal for a greater degree of uncertainty to be accepted than has been to date. Section 6.3.5 of NICE's health technology evaluations manual states: "Above a most plausible ICER of £20,000 per QALY gained, or £100,000 per QALY gained for highly specialised technologies, decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider the following factors: • the degree of certainty and uncertainty around the ICER • aspects that relate to uncaptured benefits and non-health factors • aspects that relate to health inequalities." We have outlined below our position in relation to these factors: *Uncertainty around the ICER* To resolve uncertainty we have provided the 2022 data cut with full adjustment analysis, a new TSE-IPCW approach for both 2021 and 2022 data cuts, and also the KM curves for the 4L-only data. We trust that all of this will alleviate significant uncertainty around the ICERs and therefore allow NICE to award a higher threshold than is currently in place. *Uncaptured benefits and non-health factors*

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	In the committee meeting, the patient expert specifically highlighted the value of hope for the mental health of patients and their families, noting that access to a fourth-line treatment option for advanced GIST may allow some patients to experience important life events that they might otherwise miss.[3] The value of hope and the impact this treatment could have on mental health is a significant uncaptured benefit which does not seem to have been considered and factored into the decision making appropriately, given the decision to select a threshold of [redacted] per QALY rather than the [redacted] per QALY range. *Health inequalities* Ripretinib is indicated for a **for a rare and advanced disease**, and there is high unmet medical need for this patient population after they have exhausted the approved previous treatments. We do not identify specific **inequalities** in patients with specific characteristics relative to others *within* this group (for example by sex, race or age). However, failure to recommend ripretinib may have **indirect equality implications**, including: • **Inequalities in access by geography and centre:** In the absence of a NICE recommendation for ripretinib, only patients treated at specialist centres with access to clinical trials or compassionate use programmes may be able to receive a similar therapy, potentially widening regional and socio-economic inequalities. • **Disproportionate impact on a rare, high-need group:** Adult patients with late-line GIST already face very limited options and poor prognosis after regorafenib. Restricting access to an additional active therapy has a direct impact on this small population's prognosis and treatment options, contrary to NICE's stated aim of considering greater flexibility where evidence is hard to generate. • **Mental health and caregiver burden:** Denial of an additional line of therapy is likely to worsen distress and reduce hope for patients and families; this burden falls particularly heavily on those with an advanced, life-threatening disease. These impacts are not captured in QALYs but are important from an equality and fairness perspective. We believe the preliminary recommendations may therefore **insufficiently account for the needs of a rare, high-burden population** and the broader psychosocial consequences of not providing a fourth-line option. Recognising these issues would support a more flexible, equitable interpretation of the evidence and greater acceptance of residual uncertainty in this appraisal. *Recent changes to NICE's cost-effectiveness thresholds* NICE's reference cost-effectiveness range of £20,000–£30,000 per QALY has remained unchanged in nominal terms for more than two decades, despite substantial shifts in inflation, NHS budget growth, and broader health-economic practice. On 1 December

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	2025, NICE announced that government has agreed to increase the range used in technology appraisals from £20,000 to £30,000 per QALY to £25,000 to £35,000 per QALY, with implementation planned from April 2026, subject to the necessary regulatory steps.[4] NICE has stated in the Q&A section regarding the threshold change that "Where evaluations are already underway, these will continue through our normal process. If our independent committees decide a treatment is not cost-effective using our current thresholds, and applying the new thresholds may change that decision, then the topic will be paused until NICE has the power to apply the new thresholds. Those paused topics will then be considered against the new thresholds and proceed to publication. Companies will also need to do their part by submitting their evidence to us swiftly and pricing their products fairly." The situation we are currently in could mean that the appraisal of ripretinib could be paused until NICE has the power to apply its new thresholds. In this context, applying a cost-effectiveness threshold of [redacted] per QALY to our technology raises an important issue of fairness and consistency. We do not wish to delay patient access any longer than necessary, and we also do not wish to be punished due to unfortunate timing. If the cost-effectiveness standard is set to increase imminently, applying a more restrictive threshold to this appraisal would place our submission at a disadvantage relative to future technologies that will be assessed under a more permissive benchmark. To ensure equitable treatment across technologies and to support consistent decision-making, it is therefore reasonable for this appraisal to consider the new policy and updated thresholds when interpreting cost-effectiveness results and the degree of flexibility that has currently been applied. <u>References</u> 1. Gamboa AC, Gronchi A, Cardona K. Soft-tissue sarcoma in adults: An update on the current state of histiotype-specific management in an era of personalized medicine. CA A Cancer J Clin. 2020 May;70(3):200–29. 2. Judson I, Jones RL, Wong N, et al. Gastrointestinal stromal tumour (GIST): British Sarcoma Group clinical practice guidelines. British Journal of Cancer. 2024;7(6)doi:https://doi.org/10.1038/s41416-024-02672-0 3. https://www.nice.org.uk/guidance/gid-ta11676/documents/committee-papers 4. https://www.nice.org.uk/news/articles/changes-to-nice-s-cost-effectiveness-thresholds-confirmed
11	**Uncaptured benefits of ripretinib (Draft Guidance Section 3.17)** *"The committee considered whether there were any uncaptured benefits of ripretinib. It did not identify, and the company did not highlight any additional benefits of ripretinib that were not captured in the economic modelling. So, the committee concluded that all additional benefits of ripretinib had already been taken into account."* **<u>Comment from Deciphera</u>**

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	In Section 3.1.3 of the company submission it was highlighted that the health economic analysis did not capture potential effects of the burden of advanced GIST on caregivers or of death of the patient and bereavement on caregiver and family quality of life. Data to inform on such analyses are not available but such effects are likely to exist though are not currently quantifiable. The maintenance of patients' HRQoL, including physical and role function, while receiving ripretinib suggests a potential reduction in dependence on carers, thereby also improving carer QoL. The effect of having an additional line of therapy available after regorafenib on patient QoL was also not captured due to a lack of suitable data. Having an additional therapy line would give patients hope that they can live for longer than currently possible. Hope is a factor that does not come into consideration in traditional health technology assessments (HTA); however, an ISPOR taskforce found that it has positive value, and although difficult to quantify should be considered by HTA authorities.[1] This point was also emphasised at the committee meeting and in expert statements from both the patient expert and patient group representatives. The patient expert specifically highlighted the value of hope for the mental health of patients and their families, noting that access to a fourth-line treatment option for advanced GIST may allow some patients to experience important life events that they might otherwise miss.[1] <u>References</u> 1. https://www.nice.org.uk/guidance/gid-ta11676/documents/committee-papers

Insert extra rows as needed

Abbreviation	Definition
AE	Adverse event
BID	Twice daily
BSC	Best supportive care
CI	Confidence interval
DCO	Data cut off
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EAG	External Assessment Group
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
GIST	Gastrointestinal stromal tumour
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
IPCW	Inverse probability of censoring weighting
IPD	Individual patient data
ITT	Intention to treat
KM	Kaplan Meier
KOL	Key opinion leader

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MCBS	Magnitude of Clinical Benefit Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PFS	Progression free survival
QALY	Quality adjusted life year
QD	Once daily
RCT	Randomised controlled trial
TA	Technology appraisal
TPP	Target product profile
TSD	Technical Support Document
TSE	Two stage estimation
UK	United Kingdom
WTP	Willingness to pay

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496] Response to draft guidance: Addendum containing new analysis

December 2025

File name	Version	Contains confidential information	Date
ID6496 ripretinib FORM Addendum - Draft guidance stakeholder comments form_Company response Addendum [redacted]	1.0	Yes	03 December 2025

Purpose of This Addendum

This addendum provides an update to the original consultation response submitted to the National Institute for Health and Care Excellence (NICE) regarding the draft guidance for Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments (review of TA881) [ID6496]. The updated analysis reflects a later data cut made available after the initial submission and follows NICE's requirements for clarity, transparency, and methodological alignment.

1. Company base case after consultation

The company's base case remains the same and will utilise the 2021 data cut off, using TSE, complex, generalised gamma, without recensoring and log-normal extrapolation. The patient access scheme (PAS) discount has been increased, as outlined within this document.

2. TSE IPCW

Method:
Two-stage estimation has already been performed on patients randomised to ripretinib and the complex generalised gamma model was chosen to determine counterfactual OS times (without recensoring). Instead of applying recensoring, to combine TSE with the IPCW method, counterfactual treatment start and stop times were calculated for each patient-period.

If treatment was stopped and restarted within a patient's observed data, the counterfactual treatment start time was calculated by multiplying the treatment start (during the time period) by the acceleration factor, otherwise the treatment start date remained the same. The counterfactual stop time was calculated by multiplying the difference between start and stop times by the acceleration factor.

Stabilised inverse probability weights were determined using two Cox time varying regression models to predict the probability of remaining uncensored at the end of each period. The numerator of the weight calculation adjusted for the baseline covariates (age [years]) while the denominator of the weight calculation accounted for both baseline (age [years]) and time varying covariates (ECOG at start of period, progression, EQ5D VAS at start of period and sum of lesion diameters [/100mm]). Missing covariate data was imputed as the average of all non-missing baseline values for the given time-varying covariate.

The calculated patient-time weights were then used in the calculation of parametric survival extrapolations of counterfactual OS data, in the ripretinib arm. The baseline covariates used in the calculation of stabilised weights (i.e. age (years)) were adjusted for in the weighted survival analysis. As age is a continuous variable, the covariate was centred at the mean prior to fitting to stabilise the estimation and to aid the interpretation of parameter estimates.

Justification:

Following two-stage estimation, the issue of re-censoring losing follow up time and not recensoring introducing informative bias means it is difficult to choose one of these approaches. Instead, IPCW combined with two-stage estimation is an alternative technique to address informative censoring but maintain longer term information.

Results:

The weighted counterfactual OS Kaplan-Meier curves from the TSE-IPCW analysis for 2021 are displayed in Figure 1, with the unadjusted data and modelled extrapolations. Figure 2 shows the empirical hazard, smoothed hazard and modelled hazards.

Figure 1: Overall survival (weeks)- QD to BID Crossover (Two-stage Model with IPCW: Complex, Generalised Gamma)

Figure 2: Hazard functions of observed and parametric functions for Overall Survival (Weeks)- QD to BID Crossover (Two-stage Model with IPCW: Complex, Generalised Gamma)

3. Fitting of the models to 2022 and IPCW TSE data

Parametric model selection for the 2022 data and IPCW TSE analysis was conducted in the same manner as outlined in the original company submission, taking into account visual and statistical fit as well as the plausibility of the long-term survival projections. The lognormal model was selected for ripretinib in both instances as it represents the best-fitting curves by Akaike Information Criterion [AIC], and is also consistent with the curve selected for our base case base on the 2021 data.

Goodness-of-fit statistics (AIC and Bayesian Information Criterion [BIC]) for the 2022 TSE IPDE-adjusted model fits to OS in the ripretinib arm of INVICTUS based on the 2022 data cut-off (DCO) are presented in

Table 1.

Table 1: Goodness-of-fit statistics for the parametric fits to the TSE adjusted OS models based on the 2022 data cut-off

TSE Model	Parametric model fit	AIC	BIC
Complex, Exponential, With re-censoring	Exponential	632.38	634.82
Complex, Exponential, With re-censoring	Weibull	633.55	634.82
Complex, Exponential, With re-censoring	Gompertz	634.34	639.23
Complex, Exponential, With re-censoring	Lognormal	632.57	637.46
Complex, Exponential, With re-censoring	Log-logistic	631.83	636.71
Complex, Exponential, With re-censoring	Gamma	633.16	638.04
Complex, Exponential, With re-censoring	Generalised Gamma	633.77	641.10
Complex, Exponential, Without re-censoring	Exponential	657.75	660.19
Complex, Exponential, Without re-censoring	Weibull	659.34	660.19
Complex, Exponential, Without re-censoring	Gompertz	659.67	664.55
Complex, Exponential, Without re-censoring	Lognormal	657.26	662.14
Complex, Exponential, Without re-censoring	Log-logistic	656.49	661.38
Complex, Exponential, Without re-censoring	Gamma	658.94	663.83
Complex, Exponential, Without re-censoring	Generalised Gamma	658.70	666.03
Complex, Generalized Gamma, With re-censoring	Exponential	483.34	485.79
Complex, Generalized Gamma, With re-censoring	Weibull	482.13	485.79
Complex, Generalized Gamma, With re-censoring	Gompertz	484.07	488.96
Complex, Generalized Gamma, With re-censoring	Lognormal	481.64	486.52
Complex, Generalized Gamma, With re-censoring	Log-logistic	481.02	485.91
Complex, Generalized Gamma, With re-censoring	Gamma	481.67	486.56
Complex, Generalized Gamma, With re-censoring	Generalised Gamma	483.07	490.40
Complex, Generalized Gamma, Without re-censoring	Exponential	638.09	640.53
Complex, Generalized Gamma, Without re-censoring	Weibull	639.98	640.53
Complex, Generalized Gamma, Without re-censoring	Gompertz	638.76	643.64
Complex, Generalized Gamma, Without re-censoring	Lognormal	633.90	638.79
Complex, Generalized Gamma, Without re-censoring	Log-logistic	633.58	638.46
Complex, Generalized Gamma, Without re-censoring	Gamma	639.52	644.40
Complex, Generalized Gamma, Without re-censoring	Generalised Gamma	635.90	643.23
Complex, Gompertz, With re-censoring	Exponential	632.38	634.83
Complex, Gompertz, With re-censoring	Weibull	633.55	634.83
Complex, Gompertz, With re-censoring	Gompertz	634.35	639.23
Complex, Gompertz, With re-censoring	Lognormal	632.58	637.46
Complex, Gompertz, With re-censoring	Log-logistic	631.83	636.72
Complex, Gompertz, With re-censoring	Gamma	633.16	638.05
Complex, Gompertz, With re-censoring	Generalised Gamma	633.78	641.11

TSE Model	Parametric model fit	AIC	BIC
Complex, Gompertz, Without re-censoring	Exponential	657.75	660.20
Complex, Gompertz, Without re-censoring	Weibull	659.34	660.20
Complex, Gompertz, Without re-censoring	Gompertz	659.67	664.55
Complex, Gompertz, Without re-censoring	Lognormal	657.26	662.14
Complex, Gompertz, Without re-censoring	Log-logistic	656.49	661.38
Complex, Gompertz, Without re-censoring	Gamma	658.94	663.83
Complex, Gompertz, Without re-censoring	Generalised Gamma	658.70	666.03
Complex, Log-Logistic, With re-censoring	Exponential	553.60	556.05
Complex, Log-Logistic, With re-censoring	Weibull	554.42	556.05
Complex, Log-Logistic, With re-censoring	Gompertz	555.57	560.46
Complex, Log-Logistic, With re-censoring	Lognormal	552.42	557.31
Complex, Log-Logistic, With re-censoring	Log-logistic	552.04	556.93
Complex, Log-Logistic, With re-censoring	Gamma	553.91	558.80
Complex, Log-Logistic, With re-censoring	Generalised Gamma	554.16	561.49
Complex, Log-Logistic, Without re-censoring	Exponential	647.43	649.87
Complex, Log-Logistic, Without re-censoring	Weibull	649.12	649.87
Complex, Log-Logistic, Without re-censoring	Gompertz	648.97	653.86
Complex, Log-Logistic, Without re-censoring	Lognormal	645.21	650.09
Complex, Log-Logistic, Without re-censoring	Log-logistic	644.58	649.47
Complex, Log-Logistic, Without re-censoring	Gamma	648.63	653.52
Complex, Log-Logistic, Without re-censoring	Generalised Gamma	647.03	654.36
Complex, Log-Normal, With re-censoring	Exponential	552.31	554.76
Complex, Log-Normal, With re-censoring	Weibull	552.96	554.76
Complex, Log-Normal, With re-censoring	Gompertz	554.23	559.11
Complex, Log-Normal, With re-censoring	Lognormal	551.20	556.08
Complex, Log-Normal, With re-censoring	Log-logistic	550.76	555.64
Complex, Log-Normal, With re-censoring	Gamma	552.45	557.34
Complex, Log-Normal, With re-censoring	Generalised Gamma	552.87	560.20
Complex, Log-Normal, Without re-censoring	Exponential	646.90	649.34
Complex, Log-Normal, Without re-censoring	Weibull	648.61	649.34
Complex, Log-Normal, Without re-censoring	Gompertz	648.41	653.30
Complex, Log-Normal, Without re-censoring	Lognormal	644.58	649.46
Complex, Log-Normal, Without re-censoring	Log-logistic	643.97	648.85
Complex, Log-Normal, Without re-censoring	Gamma	648.11	653.00
Complex, Log-Normal, Without re-censoring	Generalised Gamma	646.42	653.75
Complex, Weibull, With re-censoring	Exponential	632.03	634.48
Complex, Weibull, With re-censoring	Weibull	633.17	634.48
Complex, Weibull, With re-censoring	Gompertz	633.99	638.87
Complex, Weibull, With re-censoring	Lognormal	632.25	637.13
Complex, Weibull, With re-censoring	Log-logistic	631.50	636.38
Complex, Weibull, With re-censoring	Gamma	632.78	637.66
Complex, Weibull, With re-censoring	Generalised Gamma	633.43	640.76

TSE Model	Parametric model fit	AIC	BIC
Complex, Weibull, Without re-censoring	Exponential	657.58	660.02
Complex, Weibull, Without re-censoring	Weibull	659.17	660.02
Complex, Weibull, Without re-censoring	Gompertz	659.49	664.38
Complex, Weibull, Without re-censoring	Lognormal	657.06	661.94
Complex, Weibull, Without re-censoring	Log-logistic	656.30	661.18
Complex, Weibull, Without re-censoring	Gamma	658.77	663.65
Complex, Weibull, Without re-censoring	Generalised Gamma	658.51	665.84
Simple, Exponential, With re-censoring	Exponential	590.78	593.23
Simple, Exponential, With re-censoring	Weibull	591.62	593.23
Simple, Exponential, With re-censoring	Gompertz	592.69	597.58
Simple, Exponential, With re-censoring	Lognormal	590.28	595.17
Simple, Exponential, With re-censoring	Log-logistic	589.66	594.55
Simple, Exponential, With re-censoring	Gamma	591.16	596.04
Simple, Exponential, With re-censoring	Generalised Gamma	591.73	599.06
Simple, Exponential, Without re-censoring	Exponential	651.40	653.84
Simple, Exponential, Without re-censoring	Weibull	653.03	653.84
Simple, Exponential, Without re-censoring	Gompertz	653.14	658.02
Simple, Exponential, Without re-censoring	Lognormal	649.89	654.78
Simple, Exponential, Without re-censoring	Log-logistic	649.20	654.08
Simple, Exponential, Without re-censoring	Gamma	652.57	657.45
Simple, Exponential, Without re-censoring	Generalised Gamma	651.58	658.91
Simple, Generalized Gamma, With re-censoring	Exponential	469.31	471.76
Simple, Generalized Gamma, With re-censoring	Weibull	467.37	471.76
Simple, Generalized Gamma, With re-censoring	Gompertz	469.25	474.13
Simple, Generalized Gamma, With re-censoring	Lognormal	467.46	472.35
Simple, Generalized Gamma, With re-censoring	Log-logistic	466.72	471.60
Simple, Generalized Gamma, With re-censoring	Gamma	467.00	471.88
Simple, Generalized Gamma, With re-censoring	Generalised Gamma	468.68	476.01
Simple, Generalized Gamma, Without re-censoring	Exponential	636.39	638.83
Simple, Generalized Gamma, Without re-censoring	Weibull	638.32	638.83
Simple, Generalized Gamma, Without re-censoring	Gompertz	636.82	641.70
Simple, Generalized Gamma, Without re-censoring	Lognormal	631.80	636.69
Simple, Generalized Gamma, Without re-censoring	Log-logistic	631.56	636.44
Simple, Generalized Gamma, Without re-censoring	Gamma	637.88	642.76
Simple, Generalized Gamma, Without re-censoring	Generalised Gamma	633.80	641.12
Simple, Gompertz, With re-censoring	Exponential	590.79	593.23
Simple, Gompertz, With re-censoring	Weibull	591.62	593.23
Simple, Gompertz, With re-censoring	Gompertz	592.70	597.59

TSE Model	Parametric model fit	AIC	BIC
Simple, Gompertz, With re-censoring	Lognormal	590.29	595.17
Simple, Gompertz, With re-censoring	Log-logistic	589.67	594.56
Simple, Gompertz, With re-censoring	Gamma	591.16	596.05
Simple, Gompertz, With re-censoring	Generalised Gamma	591.74	599.06
Simple, Gompertz, Without re-censoring	Exponential	651.40	653.84
Simple, Gompertz, Without re-censoring	Weibull	653.04	653.84
Simple, Gompertz, Without re-censoring	Gompertz	653.14	658.03
Simple, Gompertz, Without re-censoring	Lognormal	649.89	654.78
Simple, Gompertz, Without re-censoring	Log-logistic	649.20	654.08
Simple, Gompertz, Without re-censoring	Gamma	652.57	657.46
Simple, Gompertz, Without re-censoring	Generalised Gamma	651.58	658.91
Simple, Log-Logistic, With re-censoring	Exponential	457.88	460.32
Simple, Log-Logistic, With re-censoring	Weibull	455.87	460.32
Simple, Log-Logistic, With re-censoring	Gompertz	457.71	462.60
Simple, Log-Logistic, With re-censoring	Lognormal	455.95	460.84
Simple, Log-Logistic, With re-censoring	Log-logistic	455.27	460.15
Simple, Log-Logistic, With re-censoring	Gamma	455.51	460.40
Simple, Log-Logistic, With re-censoring	Generalised Gamma	457.21	464.54
Simple, Log-Logistic, Without re-censoring	Exponential	635.56	638.01
Simple, Log-Logistic, Without re-censoring	Weibull	637.51	638.01
Simple, Log-Logistic, Without re-censoring	Gompertz	635.86	640.75
Simple, Log-Logistic, Without re-censoring	Lognormal	630.77	635.66
Simple, Log-Logistic, Without re-censoring	Log-logistic	630.58	635.46
Simple, Log-Logistic, Without re-censoring	Gamma	637.08	641.97
Simple, Log-Logistic, Without re-censoring	Generalised Gamma	632.76	640.09
Simple, Log-Normal, With re-censoring	Exponential	494.75	497.19
Simple, Log-Normal, With re-censoring	Weibull	493.50	497.19
Simple, Log-Normal, With re-censoring	Gompertz	495.40	500.28
Simple, Log-Normal, With re-censoring	Lognormal	493.18	498.06
Simple, Log-Normal, With re-censoring	Log-logistic	492.48	497.36
Simple, Log-Normal, With re-censoring	Gamma	493.05	497.94
Simple, Log-Normal, With re-censoring	Generalised Gamma	494.50	501.83
Simple, Log-Normal, Without re-censoring	Exponential	638.93	641.38
Simple, Log-Normal, Without re-censoring	Weibull	640.81	641.38
Simple, Log-Normal, Without re-censoring	Gompertz	639.71	644.60
Simple, Log-Normal, Without re-censoring	Lognormal	634.94	639.83
Simple, Log-Normal, Without re-censoring	Log-logistic	634.58	639.47
Simple, Log-Normal, Without re-censoring	Gamma	640.33	645.22
Simple, Log-Normal, Without re-censoring	Generalised Gamma	636.94	644.27
Simple, Weibull, With re-censoring	Exponential	578.36	580.81
Simple, Weibull, With re-censoring	Weibull	579.21	580.81
Simple, Weibull, With re-censoring	Gompertz	580.31	585.19

TSE Model	Parametric model fit	AIC	BIC
Simple, Weibull, With re-censoring	Lognormal	577.58	582.47
Simple, Weibull, With re-censoring	Log-logistic	577.04	581.93
Simple, Weibull, With re-censoring	Gamma	578.73	583.61
Simple, Weibull, With re-censoring	Generalised Gamma	579.16	586.48
Simple, Weibull, Without re-censoring	Exponential	650.03	652.48
Simple, Weibull, Without re-censoring	Weibull	651.69	652.48
Simple, Weibull, Without re-censoring	Gompertz	651.72	656.60
Simple, Weibull, Without re-censoring	Lognormal	648.29	653.18
Simple, Weibull, Without re-censoring	Log-logistic	647.62	652.50
Simple, Weibull, Without re-censoring	Gamma	651.21	656.10
Simple, Weibull, Without re-censoring	Generalised Gamma	650.03	657.35

TSE IPCW model fits

Goodness-of-fit statistics (AIC and BIC) for the TSE IPCW adjusted models of OS in the ripretinib arm of INVICTUS based on the 2021 and 2022 data cut -offs (DCOs) are presented in Table 22 and Table 33, respectively.

Table 22: Goodness-of-fit statistics for the parametric fits to the complex, generalised gamma IPCW TSE model based on the 2021 data cut-off

Ripretinib OS Model	Parametric model fit	AIC	BIC
2021 DCO Complex, Generalised Gamma TSE IPCW	Exponential	595.90	602.43
2021 DCO Complex, Generalised Gamma TSE IPCW	Weibull	597.82	607.63
2021 DCO Complex, Generalised Gamma TSE IPCW	Gompertz	593.82	603.63
2021 DCO Complex, Generalised Gamma TSE IPCW	Lognormal	**590.61**	**600.42**
2021 DCO Complex, Generalised Gamma TSE IPCW	Log-logistic	591.72	601.52
2021 DCO Complex, Generalised Gamma TSE IPCW	Gamma	597.87	607.68
2021 DCO Complex, Generalised Gamma TSE IPCW	Generalised Gamma	591.80	604.87

Table 33: Goodness-of-fit statistics for the parametric fits to the complex, generalised gamma IPCW TSE model based on the 2022 data cut-off

Ripretinib OS Model	Parametric model fit	AIC	BIC
2022 DCO Complex, Generalised Gamma TSE IPCW	Exponential	714.72	**721.29**
2022 DCO Complex, Generalised Gamma TSE IPCW	Weibull	716.71	726.56
2022 DCO Complex, Generalised Gamma TSE IPCW	Gompertz	714.16	724.01

Ripretinib OS Model	Parametric model fit	AIC	BIC
2022 DCO Complex, Generalised Gamma TSE IPCW	Lognormal	**712.51**	722.36
2022 DCO Complex, Generalised Gamma TSE IPCW	Log-logistic	713.41	723.26
2022 DCO Complex, Generalised Gamma TSE IPCW	Gamma	716.53	726.37
2022 DCO Complex, Generalised Gamma TSE IPCW	Generalised Gamma	714.49	727.62

4. Updated cost-effectiveness results

In the tables below the updated cost-effectiveness results based on both the 2021 and 2022 data cuts are presented, incorporating the increased PAS for ripretinib (from [redacted]% to [redacted]%) and the new TSE-IPCW scenario analysis. These demonstrate that in our revised base case ripretinib is cost-effective towards the middle of NICE's current cost-effectiveness threshold range and remains cost-effective at £30,000 per QALY in the TSE-IPCW scenario based on the 2021 data cut.

Although we consider that the 2022 data cut is less robust than the 2021 data cut for the reasons outlined in our response, ripretinib is cost-effective in all scenarios with the increased PAS under NICE's updated cost-effectiveness threshold range of £25,000 to £35,000 per QALY when applying the 2022 data cut.

Table 4: Table of cost-effectiveness results for 2021 data cut

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
Previous PAS discount ([redacted])				
Company's base case (updated; ripretinib = BID-adjusted complex gen. gamma without recensoring, lognormal; BSC = gen. gamma)	[redacted]	[redacted]	£29,350	1.7
EAG/committee preferred (ripretinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = gen. gamma)	[redacted]	[redacted]	£44,964	1.7
Updated PAS discount ([redacted])				
Company's base case (updated; ripretinib = BID-adjusted complex gen. gamma without recensoring, lognormal; BSC = gen. gamma)	[redacted]	[redacted]	£26,877	1.7
EAG/committee preferred (ripretinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = gen. gamma)	[redacted]	[redacted]	£41,035	1.7

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
TSE-IPCW scenario analysis (complex gen. gamma, lognormal; BSC = gen. gamma)	[redacted]	[redacted]	£29,282	1.7

Table 5: Table of cost-effectiveness results for 2022 data cut

Analysis	Inc. QALYs	Inc. Costs	ICER (including DM)	DM
Previous PAS discount ([redacted])				
Company's base case (updated; ripretinib = BID-adjusted complex gen. gamma without recensoring, lognormal; BSC = gen. gamma)	[redacted]	[redacted]	£34,307	1.7
EAG/committee preferred (ripretinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = gen. gamma)	[redacted]	[redacted]	£37,235	1.7
Updated PAS discount ([redacted])				
Company's base case (updated; ripretinib = BID-adjusted complex gen. gamma without recensoring, lognormal; BSC = gen. gamma)	[redacted]	[redacted]	£31,371	1.7
EAG/committee preferred (ripretinib = BID-adjusted complex gen. gamma with re-censoring, log-logistic; BSC = gen. gamma)	[redacted]	[redacted]	£34,026	1.7
TSE-IPCW scenario analysis (complex gen. gamma, lognormal; BSC = gen. gamma)	[redacted]	[redacted]	£31,728	1.7

5. 4L only and 4L+ analysis

Method: KM curves were generated for OS, PFS and the composite of progression or discontinuation to compare patients receiving ripretinib in true fourth line, those treated after four or more prior lines and the overall ripretinib cohort. Survival times for subjects randomised to ripretinib were adjusted for IPDE (TSE, complex, gen. gamma, with and without recensoring) and survival times for subjects randomised to placebo adjusted for ripretinib QD switching (TSE, simple, log-logistic, with recensoring). These analyses have been performed in a simple way by subgrouping the counterfactual data after the TSE has been applied, so this assumes that the effect of switching on post-progression survival is the same regardless of how many prior lines of therapy a patient has received. This assumption avoids the problem of having too few patients in each subgroup for more complex switching adjustments.

Justification: The INVICTUS study population included patients who had received four or more prior lines of therapy, raising concerns regarding the generalisability of the trial results, where if ripretinib was routinely available in NHS clinical practice, patients would likely switch to it as a fourth-line option immediately after progression on regorafenib. This additional analysis, which incorporates treatment switching adjustments, directly addresses the uncertainty in Draft Guidance Section 3.12 by providing treatment effect estimates that are representative of patients who would receive ripretinib in true fourth line.

Results: [redacted]

2021 DCO

Overall survival

Figure 3a: Kaplan-Meier plot of time from randomisation to death, by number of prior therapy lines, ITT subjects (N=129)

Figure 3b: Kaplan-Meier plot of time from randomisation to death, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Figure 4a: Kaplan-Meier plot of time from randomisation to death, by number of prior therapy lines, ITT subjects (N=129)

Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, with recensoring [EAG/committee base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, with recensoring [EAG/committee base case])

Figure 4b: Kaplan-Meier plot of time from randomisation to death, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, with recensoring [EAG/committee base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, with recensoring EAG/committee base case])

Figure 4c: Kaplan-Meier plot of time from randomisation to death, by number of prior therapy lines, ITT subjects (N=129)

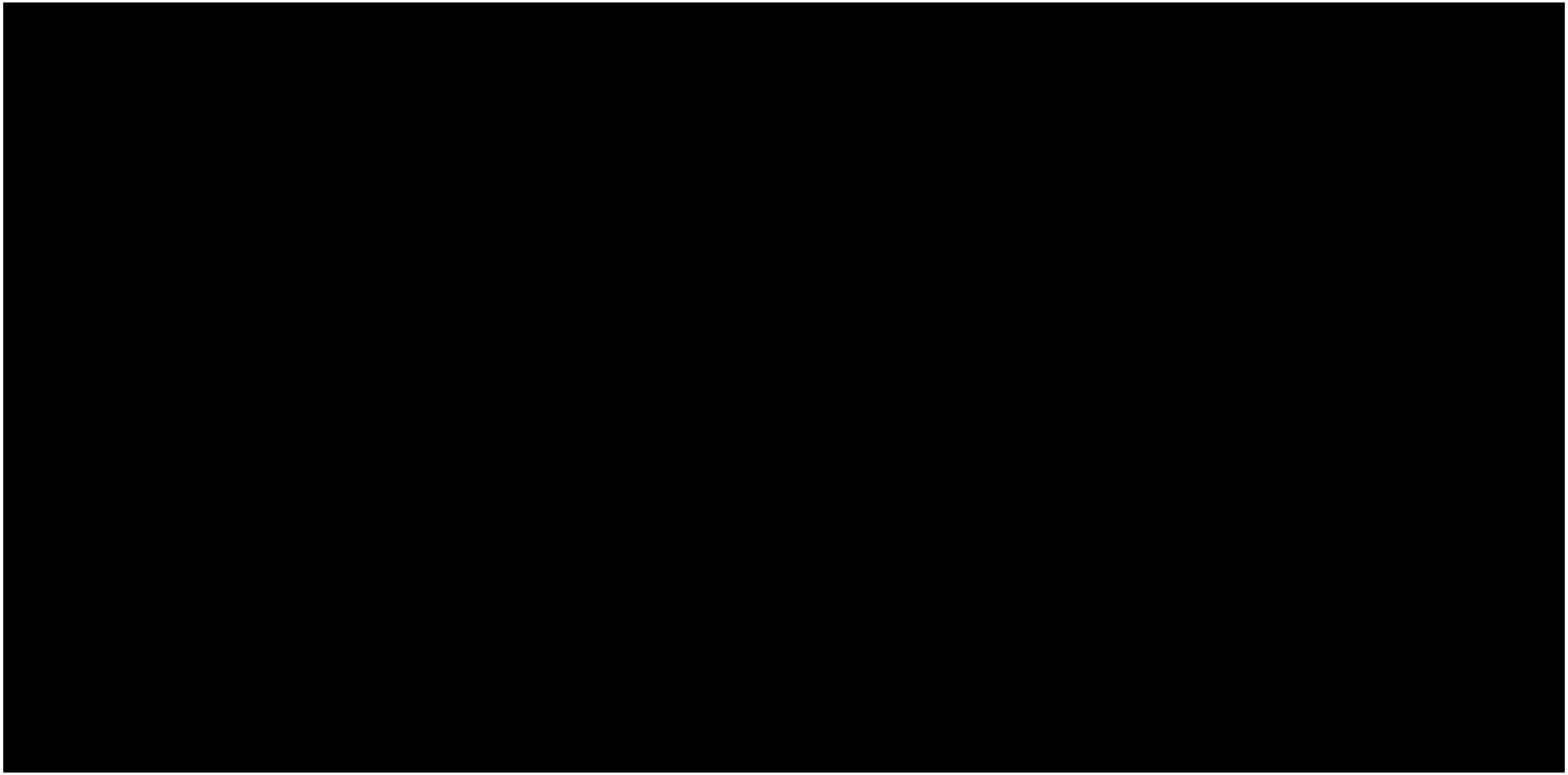
Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, without recensoring [EAG/committee base case)

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, without recensoring [EAG/committee base case)

Figure 4d: Kaplan-Meier plot of time from randomisation to death, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, without recensoring [company base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, without recensoring [company base case])



Progression-free survival

Figure 5a: Kaplan-Meier plot of time from randomisation to PFS, by number of prior therapy lines, ITT subjects (N=129)

Figure 5b: Kaplan-Meier plot of time from randomisation to PFS, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Figure 6a: Kaplan-Meier plot of time to composite of progression & discontinuation of Ripretinib any dose, by number of prior therapy lines, Subjects randomised to Ripretinib (N=85)

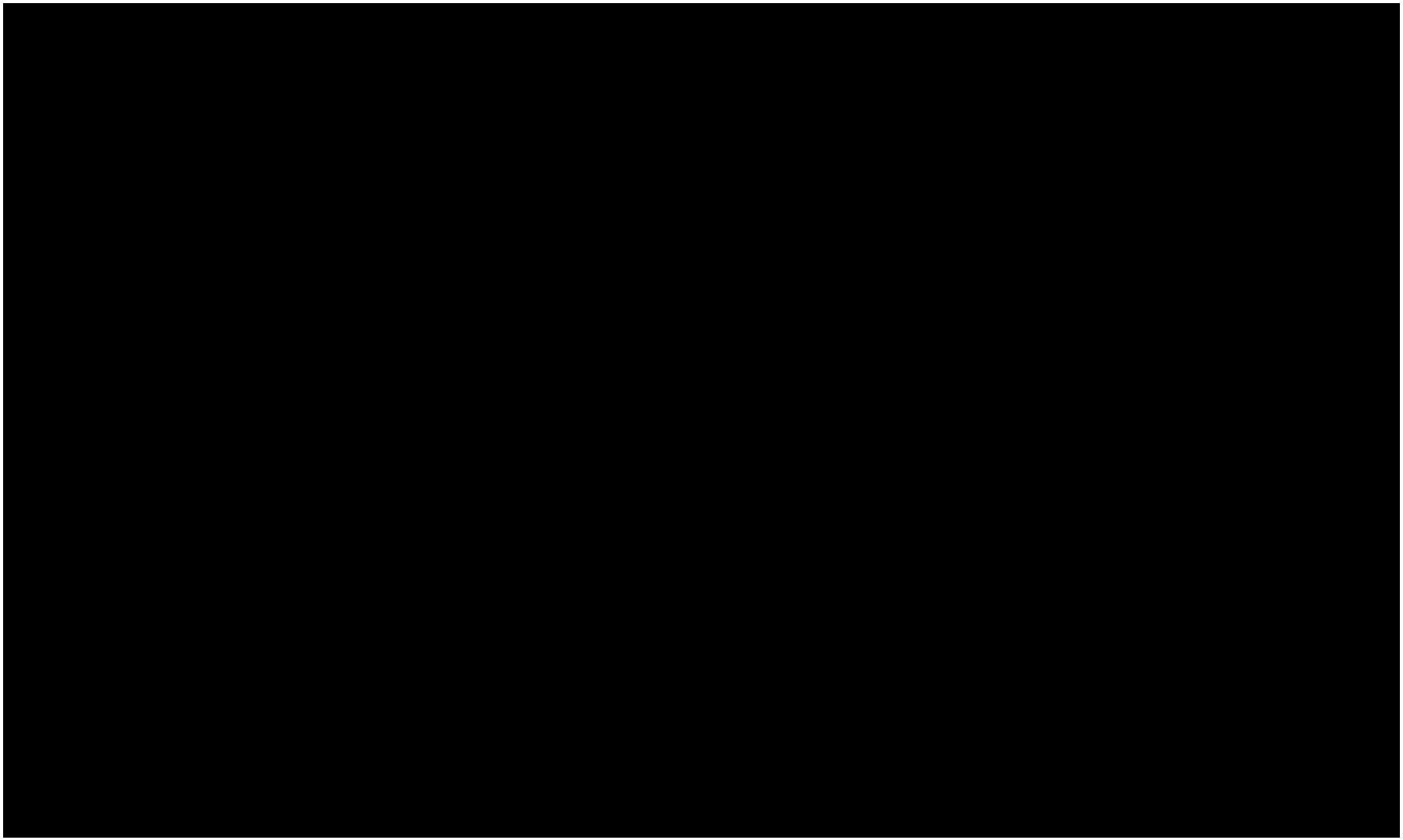


Figure 6b: Kaplan-Meier plot of time to composite of progression & discontinuation of Ripretinib any dose, overall and for subjects with 3 prior therapy lines, Subjects randomised to Ripretinib (N=85)

2022 DCO

Overall survival

Figure 7a: Kaplan-Meier plot of time from randomisation to death, by number of prior therapy lines, ITT subjects (N=129)

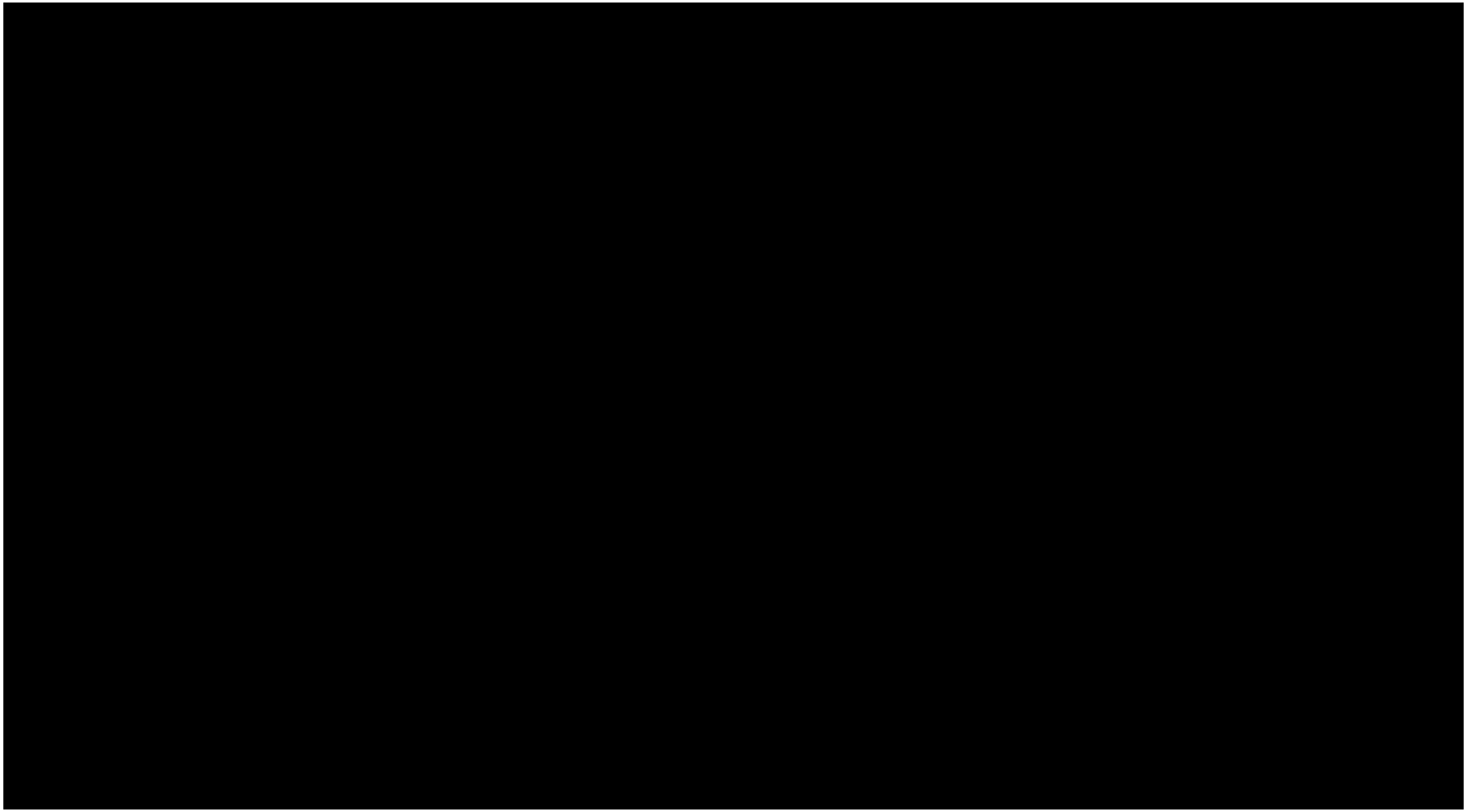


Figure 7b: Kaplan-Meier plot of time from randomisation to death, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Figure 8a: Kaplan-Meier plot of time from randomisation to death, by number of prior therapy lines, ITT subjects (N=129)

Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, with recensoring [EAG/committee base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, with recensoring [EAG/committee base case])

Figure 8b: Kaplan-Meier plot of time from randomisation to death, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, with recensoring [EAG/committee base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, with recensoring [EAG/committee base case])

Figure 8c: Kaplan-Meier plot of time from randomisation to death, by number of prior therapy lines, ITT subjects (N=129)

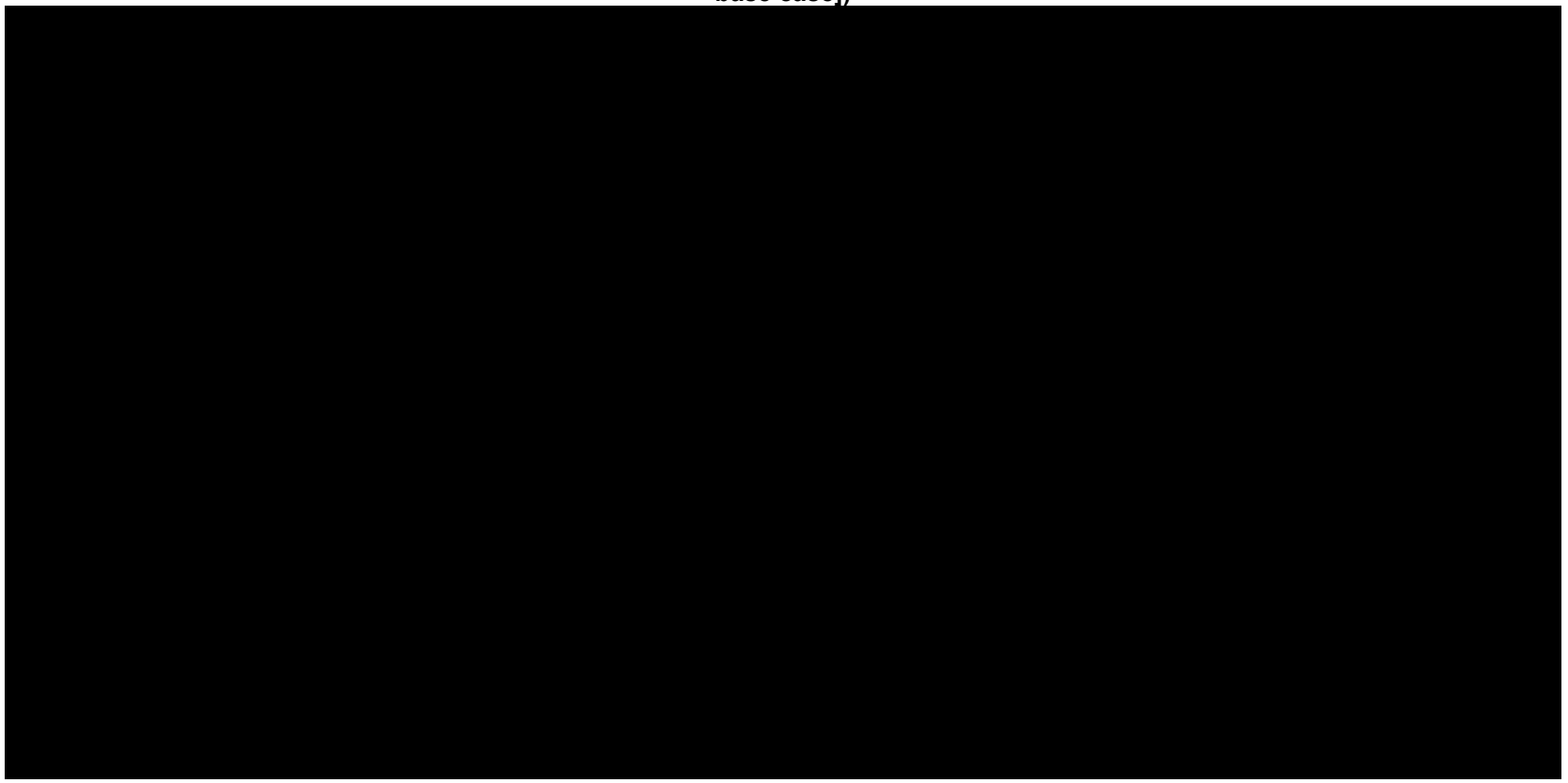
Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, without recensoring [company base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, without recensoring [company base case])

Figure 8d: Kaplan-Meier plot of time from randomisation to death, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Survival times for subjects randomised to Ripretinib adjusted for IPDE (TSE, complex, gen. gamma, without recensoring [company base case])

Survival times for subjects randomised to placebo adjusted for Ripretinib QD switching (TSE, simple, log-logistic, without recensoring [company base case])



Progression-free survival

Figure 9a: Kaplan-Meier plot of time from randomisation to PFS, by number of prior therapy lines, ITT subjects (N=129)

Figure 9b: Kaplan-Meier plot of time from randomisation to PFS, overall and for subjects with 3 prior therapy lines, ITT subjects (N=129)

Figure 10a: Kaplan-Meier plot of time to composite of progression & discontinuation of Ripretinib any dose, by number of prior therapy lines, Subjects randomised to Ripretinib (N=85)

Figure 10b: Kaplan-Meier plot of time to composite of progression & discontinuation of Ripretinib any dose, overall and for subjects with 3 prior therapy Lines, Subjects randomised to Ripretinib (N=85)

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 December 2025.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	GIST CANCER UK

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 December 2025.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NONE
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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

Draft guidance comments form

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1	We submit these comments as a patient advocacy organization representing GIST patients across the UK. We are not health economists or clinical trial experts. Our perspective is that of patients and families facing this disease. Our core position is that (1) the evidence for Ripretinib, while acknowledged to have limitations, is sufficient - as demonstrated by approval in Scotland, France, Germany, and other comparable healthcare systems; (2) the limitations in evidence are inherent to studying terminal cancer patients at 4th-line therapy, not a failure of trial design; (3) the choice is between uncertain benefit and certain death - there are no alternative treatments after Regorafenib failure; and (4) England and Wales patients are being unfairly disadvantaged compared to Scottish patients.
2	No, we do not feel all of the relevant evidence has been taken into account because: **Divergence from decisions of committees of similar standing:** We do not feel that the committee has examined in full, the evidence that has led other countries to provide this drug to patients. The committee must justify why its judgment as to whether to recommend Ripretinib or not diverges from the conclusions drawn by committees of similar stature, expertise, and financial capacity as your own, for example Scotland, France, Germany. Unless the Committee has examined the data and deliberations of these groups and is able to justify publicly and in a clear and transparent fashion why their opinion differs, we cannot consider that all of the relevant evidence has been examined. We respectfully seek clarification on why the cost-effectiveness assessment differs from assessments conducted by similar HTA bodies in Scotland, France, and Germany, particularly given comparable healthcare budgets and patient populations
3	**Economic benefit of reduced drug side effects:** Patients reaching 4th-line therapy have often experienced significant toxicity from prior treatments. The tolerability profile of Ripretinib is particularly important for this population because they have limited physiological reserve, quality of remaining life is paramount, and treatment discontinuation due to toxicity means no alternatives remain. We note that patient-reported outcomes and quality of life data may not fully capture the value patients place on avoiding treatment-related hospitalization and severe toxicity at this stage of disease. Many people continue with paid work and unpaid work as carers and parents throughout treatment on Imatinib but are not able to do so on sunitinib or Regorafenib. These people may be able to return to some degree of work or economic productivity on this drug. The committee must explicitly include the economic benefits of the reduced side effects in its calculations.
4	**Fairness to patient who cannot tolerate first, second- and third-line treatment due to toxicity:**

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	The analysis of cost effectiveness has not specifically examined the case of patients who cannot tolerate 2nd and 3rd line treatment due to toxicity. As a second line therapy, Ripretinib has comparable efficacy to sunitinib with a favourable safety profile (Bauer et al, J Clin Oncol 2022). Therefore, the Committee should consider funding Ripretinib for patients who are unable to tolerate Sunitinib or Regorafenib due to toxicity. These patients are often healthier and earlier on in their disease process and would expect to gain a much greater survival benefit than patients who have exhausted second- and third-line tyrosine kinase inhibitors. Moreover, for such patients, the NHS does not incur the cost burden of Sunitinib or Regorafenib and therefore in the interests of fairness, their health economic case should be judged differently. We formally request that the committee conduct a subgroup cost-effectiveness analysis for patients who require third-line therapy but discontinued second-line therapy due to intolerance (not disease progression). This population has different clinical characteristics and cost profiles that warrant separate evaluation.
5	**Use of Ripretinib as second-line in patients with Sunitinib- or Regorafenib-refractory mutations** The Committee has not specifically examined the case of patients who require a second line treatment but are known to have mutations that render Sunitinib and Regorafenib less effective. In current practice, these patients are given Sunitinib and the Regorafenib anyway due to lack of alternatives and have poor outcomes. These patients would derive a greater overall survival benefit from Ripretinib and therefore the cost-effectiveness calculation for this specific subgroup would be different.
6	**Inclusion of personalised medicine benefits and savings in cost-effectiveness calculation** We note that In Section 3.17 section" Uncaptured benefits", the draft guidance states: *"The committee considered whether there were any uncaptured benefits of Ripretinib. It did not identify, and the company did not highlight any additional benefits of Ripretinib that were not captured in the economic modelling. So, the committee concluded that all additional benefits of Ripretinib had already been taken into account"* We do not agree that this is the case. Given the advances in personalised medicine and the ability to discriminate between GIST patients based on individual mutational status, it is surprising and disappointing that the Committee has not given this aspect even a cursory glance. There is clear evidence to show that different tyrosine kinase resistance mutations respond differently to specific tyrosine kinase resistance mutations. For example, in the INTRIGUE trial, patients with primary *KIT* exon 11 mutations and secondary mutations exclusively in exon 17/18 detected in ctDNA had a significant improvement in median PFS when treated with Ripretinib compared with sunitinib (14.2 vs. 1.5 months; nominal $p < 0.0001$). (Reference Larrain et al, Ann Surg Oncol Feb 2025).

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	The current algorithm for tyrosine kinase inhibitor use is to use one drug until it fails, then move to the next one in the order of imatinib to sunitinib (second line), regorafenib (third line), and then potentially Ripretinib. This order is not a scientifically chosen one, it is a historical legacy of the original order in which these drugs received FDA approval. The trials on which use of these agents were based did not include mutational status and included GIST patients with a whole range of mutations, almost definitely including mutations likely to be resistant to TKI therapy. The inclusion of an unknown number of patients with refractory resistance mutations means that the overall survival benefit for patients with genuinely susceptible mutations is under-estimated in the INVICTUS and other trials. Since it is now common-place and feasible to determine the exact resistance mutations involved, the potentiation of overall survival benefit in patients with Ripretinib susceptible mutations should be reflected in the cost-benefit analysis. Additionally, the NICE Committee appraisal states that "Regorafenib may not be given if testing has suggested that there is a mutation that means it will not be effective". The cost-benefit analysis must also factor this in. 1. (Para 3.9) If the decision modifier (and other model inputs) are based on the INVICTUS population, which is a sicker population than would be expected to have Ripretinib in current clinical practice, does that mean that in practice the real regorafenib treatment group are healthier at baseline and would live longer on regorafenib and get better cost effectiveness from the drug? How would this affect the QALY calculation? 2. "A clinical expert explained that people having later lines of treatment for GIST are now generally fitter than they used to be at the same stage in the treatment pathway." We request that the Committee explain how this has been reflected in the QALY calculation. 3. We note that as per page 38 of the Committee Papers, time to treatment discontinuation (TTD) was undertaken post-hoc to provide data on continued treatment post-progression required for the cost-effectiveness model. Ripretinib beyond diseases progression (TBP, page 44). We seek clarification on and the appropriateness of this calculation. Whilst the Committee notes on page 73 of the Committee Papers that it believes that the proportion and duration of patients remaining on treatment after progression reflects that of expected UK practice as guessed at by clinician experts, there is no hard evidence to support or quantify this time period. Cost effectiveness is necessarily different once a drug has started to fail, but the loose and inaccurate estimation of this time period means that GIST patients are currently receiving no 4th line drug at all, rather than at least being funded until disease progression. This is an unacceptable compromise. We request that the Committee calculate the cost-effectiveness of Ripretinib without including time

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	on Ripretinib beyond disease progression (TBP) and calculate the cost of funding Ripretinib in the TBP period separately so the value of each can be assessed more clearly. The cost of funding Ripretinib beyond disease progression could be assessed separately and if necessary, consideration could be given to funding only to disease progression or a fixed period beyond.
7	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** 1. No, for the reasons above.
8	**Are the recommendations sound and a suitable basis for guidance to the NHS?** 1. No, for the reasons above.
10	Scotland vs England/Wales Inequality: The Scottish Medicines Consortium (SMC) accepted Ripretinib on 11th August 2025. NHS Scotland has been providing Ripretinib to eligible patients since then. NHS England and NHS Wales have no approved access route. This creates geographic health inequality: • A patient living in Edinburgh: Can access Ripretinib • A patient living in London: Cannot access Ripretinib • Same disease, same evidence, same NHS system We respectfully request that NICE explain why its determination differs from SMC, given both are evaluating NHS cost-effectiveness in UK populations.
11	In addition to above, this recommendation does not consider the Rare Cancers Bill (Dr Scott Arthur MP) which has passed through the commons and is currently at its second reading in the House of Lords. This Bill not only means that more research is done into Rare Cancers, but also patients are able to access new treatments. Currently in the UK there are only 3 lines of approved treatment for GIST Cancer and the evidence shown in America and Europe indicate that Ripretinib would be a viable 4th line of treatment. We feel that the committee should consider whether Ripretinib should be made available using the Cancer Drug Fund available in England and Wales for some patients who have reached the end of other available treatments.
12	As a patient advocacy organisation, we find it difficult to understand the technical details of the cost-effectiveness assessment. However, we note that Scotland, France, and Germany reviewed the same evidence and reached different conclusion. We cannot see why their decision diverges from that of multiple committees of similar standing and economic resources, including Scotland, France and Germany. We request that NICE provide transparency on:

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	1. Why the cost-effectiveness determination differs from Scotland, France, and Germany 2. What specific parameters drove this difference 3. What evidence or conditions would be required for approval In addition to disagreeing with the health economic case made against Ripretinib by the NICE Committee, we are disappointed by the very narrow scope of the appraisal, which ignores all of the hard-won progress in personalised medicine in the field of GIST treatments and fails to examine any of the questions it raises. For example, should patients with specific Ripretinib-susceptible mutations actually have Ripretinib as a second line drug rather than fourth line? Should patients who cannot have Sunitinib/Regorafenib at all due to toxicity should be funded to receive Ripretinib as a second line? Currently, usage of tyrosine kinase inhibitors follows a set algorithm- first imatinib, then if that fails, sunitinib, then if that fails, Regorafenib, and if that fails, then potentially Ripretinib. This order not based on scientific reasoning, it is in fact based on the historical order in which these agents were approved by the FDA. Thus, the current algorithm of tyrosine kinase inhibitor usage is antiquated. We understand the committee may view treatment sequencing decisions as outside the scope of this specific appraisal. However, we believe these considerations are relevant to understanding why patients and clinicians view Ripretinib as an important treatment option, and why inflexible sequential approaches may not serve patients' best interests. Summary and Path Forward: We recognize the committee has concerns about the evidence base and cost-effectiveness. However, we believe these concerns must be balanced against: 1.The reality of the patient population: These are terminally ill patients with no alternatives. Evidence limitations are inherent to studying this population. 2.International precedent: Scotland, France, and Germany found the evidence sufficient under similar economic constraints. 3.The choice patients face: This is not uncertainty vs. certainty - it's uncertain benefit vs. certain death. 4.Equity considerations: England and Wales patients deserve the same access as Scottish patients. **We respectfully request that the committee:** Reconsider the appraisal in light of and provide clear specific guidance on: • End-of-life criteria applicability • What evidence would be sufficient for approval in this population • Inherent evidence limitations in terminal, rare disease populations • International HTA body precedent

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	• Whether the Rare Cancers Bill considerations apply • Whether Cancer Drugs Fund entry is feasible • What cost-effectiveness threshold or conditions would be acceptable • The reality that no alternative treatments exist Patients with GIST currently have access to only 3 lines of therapy in England and Wales. They cannot wait indefinitely for perfect evidence that may never be achievable in terminal, rare disease populations."
13	**Questions for Committee Response** We request the committee specifically address the following questions in the Final Appraisal Determination: 1. Scotland Comparison: •Scotland reviewed the same evidence and approved Ripretinib •What specifically in NICE's methodology leads to a different conclusion? •Is it appropriate for English/Welsh patients to have different access than Scottish patients? 2. Evidence Standards: •What level of evidence WOULD be sufficient for 4th-line approval in a rare cancer? •Has NICE approved other 4th-line cancer therapies with similar evidence? •Is NICE requiring evidence that is impossible to generate in terminal, rare disease populations? 3. End-of-Life Criteria: •Were end-of-life criteria (life expectancy <24 months, small population, no alternatives) considered? •If not, why not? •If yes, which criteria were not met? 4. Patient Alternative: •What should oncologists tell patients who have failed 3 lines of therapy? •How does denying this treatment serve these patients' interests? We believe patients and stakeholders deserve clear, specific responses to these questions.

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	PAWS-GIST

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are devastated by the current recommendations made in the draft guidance.
2	During the committee meeting we were concerned that the committee focused heavily on the subject of “double dosing”. We realise that the main point of issue is cost but wish for the appraisal

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	to focus on approval of Ripretinib "within" its marketing authorisation, which is "one dose daily" and not de-rail the whole appraisal with double dosing which is not part of the marketing authorisation.
3	Section 3.1 of the draft guidance is rather confusing. Paragraph 2 which starts on page 6 needs to be amended as follows to be an accurate reflection of what happens when a GIST patients' cancer progresses beyond the control of third-line treatment regorafenib: *"But when the three approved lines of treatment stop working it is because the cancer has developed new mutations that are resistant to the treatment. Most commonly the resistance mutations that develop are in exons 17 and 18. Currently the only option for patients in this situation is best supportive care or, if available a clinical trial. Ripretinib has been developed specifically to target mutations in exons 17 and 18 and is much easier to tolerate than other TKI's in the series. A patient expert explained…." Etc.*
4	In section 3.14. it states that the company is proposing an ICER which is within the range that NICE considers acceptable. The EAG analysis produces an ICER which is not considered cost effective. The EAG analysis used re-censoring and log-logistic extrapolation producing results that are different to the company's results because different methods have been used. Is it not possible for the committee and the company to agree one method of statistical analysis to determine the cost of "single dose" Ripretinib and then if the cost exceeds the acceptable ICER, agree some kind of calibration of costs to be geared by the company to maintain an ICER that I acceptable?
5	**Has all the relevant information been taken into account?** Please make it clear that disease progression happens because mutations occur in exons 17 & 18 and that Ripretinib has been designed specifically to target these mutations.
6	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Clinical effectiveness of single use Ripretinib is summarised as being statistically significantly longer than placebo in 2019, 2020 & 2021. It shows overall survival of 15.1 compared to 6.6 months in placebo and 11.6 compared to 1.8 months in the crossover group. We are unsure why in the cost effectiveness section it appears not to use the same single use data.
7	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The recommendations are hugely disappointing. Ripretinib is recognised to provide significant benefit to patients whose GIST cancer has progressed beyond the control of the current three approved TKI's for GIST. Different statistical modelling approaches are seemingly making it impossible for the company and the committee to agree. Has the company agreed the logic of including recensoring and applied log-logistic analysis to the data and if so, does it produce the same result and make sense to them to do this?

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	Is it not possible for the committee and company to agree one method of statical analysis that can be used to determine the cost of “single dose” usage of Riretinib?

Insert extra rows as needed

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Dr Charlotte Benson , Consultant Medical Oncologist, Royal Marsden Hospital

- **Has all the relevant evidence been taken into account?**

I am concerned that the discussion during the first appraisal meeting focused on Ripretinib given twice and its costings. It is important to note that the approved dose is Ripretinib 150 mg once a day and this would be our dose in clinical practice in England.

The INVICTUS trial clearly demonstrated

1. Ripretinib is well tolerated with acceptable side effects profile.
2. The median PFS of 6.3 months is clinically significant in a 4th line (or beyond) setting in GIST patients. The median PFS for Sunitinib in 2nd line setting was under 7 months and Regorafenib in 3rd line setting was 4.8 months.
3. The median PFS for patients on placebo was < 2 months. This fits with my experience in real life with all the kinase inhibitors in GISTs. Patients progress quickly after cessation of treatment. Imatinib 4th line is of negligible benefit

The real-life data from the Royal Marsden hospital: (Lim, S.Y.; Efficacy and Safety of Ripretinib in Advanced Gastrointestinal Stromal Tumours within an Expanded Access Program: A Cohort Study. Cancers 2024, 16, 985.https://doi.org/10.3390/cancers16050985) confirmed the benefits of Ripretinib 150 mg once a day with a PFS of 7.9 (95% CI 5.6–19.3) months. My personal experience is that it is better tolerated than both Sunitnib and Regorafenib in clinical practice.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of evidence?**

1. Regarding the estimated 10-year overall survival as stated in the consultation meeting I estimate this to be in the order to 5-6%.

Given the superior toxicity profile of Ripretinib to both Suntinib and Regorafenib, and my own experience of treating patients on Ripretinib, patients have experienced prolonged benefit on this drug . As side effects are less than Sunitinib/Regorafenib it easier to maintain a meaningful therapeutic dose and preserve performance status and quality of life. Furthermore, there are several GIST trials in the pipeline which are likely to extend survival further beyond 4th line but this can only be an option for patients that are clinically stable.

2. In the current situation, patients are being maintained on Regorafenib for longer periods (i.e. beyond progression) that we would like and are getting deconditioned and often experiencing severe side effects due to the absence of 4th line treatment. The option of switching to Ripretinib on progression when patients are fitter would likely translate in to further overall survival benefits

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

1. I believe the initial outcome of not recommending Ripretinib for use in NHS England is not the correct one.
2. The INVICTUS trial was a huge global effort between GIST specialists which has led to approval of Ripretinib in Europe and USA and Ripretinib is now in all the International GIST guidelines. There is unlikely to be a further trial of greater magnitude to explore any queries raised in this NICE appraisal. I am very concerned that if Ripretinib is not approved now it is very unlikely to be reappraised in the light of (non-forthcoming) new evidence.
3. Patients who progress on Sunitinib/Regorafenib often have secondary mutations in exon 17/18 in KIT gene in their tumours. Ripretinib is the most effective drug that targets these resistant mutations. Further targeted research is ongoing to characterise this. Knowledge of these resistance mutations means that clinicians should be able to choose Ripretinib in those very specific circumstances that we know it to be beneficial ie

precision medicine and conversely not for other patients- demonstrating rational and cost effective prescribing in the NHS

- **Unlawful discrimination against certain groups;**

1. There will be a disparity between what patients with GIST in England and patients in Scotland can receive as treatment now that the SMC has approved the use of Ripretinib
2. If Ripretinib is not approved treatment options for patients with GIST in England will be severely curtailed and out of step with Europe and USA

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Comments from Dr V Ramesh Bulusu

- **Has all the relevant evidence been taken into account?**

I strongly feel that the discussion during the first appraisal meeting was heavily weighted on the twice daily dose Ripretinib and its costings. The approved dose (FDA, EMA and MHRA) is Ripretinib 150 mg once a day. The observations worth highlighting from the INVICTUS trial are

1. Ripretinib is well tolerated with acceptable side effects profile.
2. The median PFS of 6.3 months is remarkable in a 4th line (or beyond) setting in GIST patients. The median PFS for Sunitinib in 2nd line setting was under 7 months and Regorafenib in 3rd line setting was 4.8 months.
3. As expected, the median PFS for patients on placebo was < 2months. This has been our experience in real life with all the kinase inhibitors in GISTs. Patients progress rapidly once we stop the treatment.

The real-life data from the Royal Marsden hospital: (Lim, S.Y.; Efficacy and Safety of Ripretinib in Advanced Gastrointestinal Stromal Tumours within an Expanded Access Program: A Cohort Study. Cancers 2024, 16, 985.https://doi.org/10.3390/cancers16050985) confirmed the benefits of Ripretinib 150 mg once a day with a PFS of 7.9 (95% CI 5.6–19.3) months. There were no red flags from the toxicity point of view.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of evidence?**

1. The 10-year overall survival probability of 2%, I believe is a very low and pessimistic estimate. The reality is that the figure is likely to be closer to 5-6%. When a further line of therapy is available, we tend to switch to next line as quickly as possible when the patient is fit and well to get the best benefit of the subsequent line of therapy. We have observed this with Sunitinib and Regorafenib.
2. It is worth remembering that the 4th line therapy in metastatic gists is an end-of-life treatment. There are no further lines of therapy

as of 2025. The recommendation on progression following Ripretinib treatment is either best supportive care or in a few selected patients who can access a clinical trial, to enrol in a clinical trial. I would like the committee to take this into consideration when discussing the ICER cut off values.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

1. We as the GIST community treating this rare cancer, are very disappointed with the initial outcome of not recommending Ripretinib for use in NHS England.
2. There will not be another trial with larger number of patients to address any uncertainties highlighted during the discussion.
3. Patients who progress on Sunitinib/Regorafenib often have secondary mutations in exon 17/18 in KIT gene in their tumours. Ripretinib is the most effective drug so far targeting these resistant mutations.
4. We strongly believe that Ripretinib should be made available for gist patients in NHS England.
5. Scottish Medicines Consortium has already approved Ripretinib in Scotland. There is now a gross disparity of access within the United Kingdom.

- **Unlawful discrimination against certain groups;** NO

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Consultation on the draft guidance document – deadline for comments 5pm on 3 December 2025.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Patient Expert - Fiona Newton

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 3 December 2025.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None to disclose
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to disclose
Name of commentator person completing form:	Fiona Newton

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I feel that the committee's decision does not support the unmet need of patients with Exon 17/18 for whom Ripretinib would be particularly effective in increasing progression free survival and overall survival. It has been shown that this group of patients do not respond to the current 2nd line

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	treatment of Sunitinib, so couldn't the cost saving on Sunitinib simply be transferred to Ripretinib? Similarly, the committee decision does not take account of the unmet need of patients who cannot tolerate Sunitinib and/or Regorafinib. In these cases, Ripretinib could be used as 2nd or 3rd line treatment and the cost saving would come from not using the other drugs. Having Ripretinib as an available option for these patient cohorts would make a significant difference as they are currently disadvantaged. In this respect, I believe the committee's decision is not good advice for NHS clinicians as it severely compromises their treatment options for these groups of patients.
2	I feel that not enough weight was given to the clinical experts' evidence in the committee meeting. They have the real-life experience of using the drug in the field and have seen firsthand the difference it can make to patient's lives. The clinicians felt that patients now coming to Ripretinib are generally fitter than in previous years due to advances in treatment care and that overall survival was better than the statistical model showed. They noted that patients on Ripretinib also have less side effects than on Sunitinib and Regorafinib and this in turn can bring an economic cost saving which has not been considered.
3	The decision of the committee is not in line with the recent Rare Cancers Bill that has recently gone through the House of Commons. The aim of the Bill is to increase research into rarer cancers and to improve access to clinical trials for patients with rarer cancers. However, these efforts will be stymied if the drugs are not approved by NICE once they have been proven to be effective. Even if we accept that the cost per QALY may be slightly above the usually accepted range (which is still a point of debate), the nature of a rare cancer like GIST is that only relatively small numbers of patients will be accessing it. I don't believe this has been taken into account.
4	If more statistical data is needed, then at the very least, the drug should be made available via the Cancer Drugs Fund whilst more evidence is gathered i.e. there are still the results of the INSIGHT trial yet to come which will provide more evidence of the drug's efficacy, particularly in relation to patients with exon 17/18 mutations.
5	In terms of issues of inequality, it seems an obvious point of inequality that this drug should be available and accessible to one part of the United Kingdom but not another. That seems fundamentally unjust. How can it be right that patients in Scotland can have access to this life extending treatment but not in England? There are many campaigns underway to try and address postcode inequality, but the committee's decision stands in the face of this.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and

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

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separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

a. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I've had Gist for 13 years I've worked through out all 3 treatments for gist. I can not believe that this drug is available in Scotland that is 200 miles away and not in England and it is due to cost. I feel I've paid my taxes all my life and I should be able to get this on the nhs.
I've been given 3-6 months to live I've had growth on my last 4 ct scans and this is my only lifeline I'm a 59 year old female who is not willing to give up. I have 2 grandchildren that dote on me I can not leave them.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

a. Has all of the relevant evidence been taken into account?

No.

b. Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

No.

c. Are the recommendations sound and a suitable basis for guidance to the NHS?

The statements made by NICE are not supported by evidence. The evidence base for ripretinib as fourth line therapy in advanced GIST is

robust with a randomized trial clearly meeting the primary endpoint.
1. Overall survival was not the primary end point of the trial, and the trial had a crossover design for ethical reasons.
2. There is NO evidence to support the statement "Uncertainty in generalisability to the population that would have Qinlock® in NHS clinical practice". As an NHS hospital we were one of the top recruiters onto the trial and consequently reflective of NHS practice. The statement regarding "generalisability" could be used for any "clinical trial".
3. There is NO evidence to support the statement: "Patients in the INVICTUS trial were sicker and had different prior treatment sequences." This is opinion. There is more evidence indicating that patients not treated on the Invictus trial were sicker.
4. There is NO evidence to support the statement "Outcomes have since improved in real-world practice, making trial results less directly applicable". This unsupported opinion.

d. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The statements made by NICE are not supported by evidence. The evidence base for ripretinib as fourth line therapy in advanced GIST is robust with a randomized trial clearly meeting the primary endpoint.
1. Overall survival was not the primary end point of the trial, and the trial had a crossover design for ethical reasons.
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4. There is NO evidence to support the statement "Outcomes have since improved in real-world practice, making trial results less directly applicable". This unsupported opinion.

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

Addendum: EAG critique of the company's response to the NICE draft guidance

Authors	Paul Tappenden, Professor of Health Economic Modelling, SCHARR, University of Sheffield, Sheffield, UK Jen-Yu Amy Chang, Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Kate (Shije) Ren, Professor of Statistical Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
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Date completed	16th December 2025

1. Introduction

In October 2025, the National Institute for Health and Care Excellence (NICE) published a negative draft recommendation for ripretinib for the treatment of advanced gastrointestinal stromal tumour (GIST) in adults after 3 or more kinase inhibitors, including imatinib.[1] The NICE Draft Guidance (DG) highlights uncertainties relating to the adjustment of overall survival (OS) estimates for people who dose-escalated to receive ripretinib 150mg twice daily (BID) and around long-term expectations of OS in the target population for ripretinib. The NICE DG states that the Appraisal Committee's preferred assumptions were in line with the External Assessment Group's (EAG's) preferred analysis. This analysis included the use of the two-stage adjustment method (complex, generalised gamma model to estimate the counterfactual OS, with re-censoring) and the use of the log-logistic distribution for extrapolation in the ripretinib group. The EAG's preferred analysis resulted in an incremental cost-effectiveness ratio (ICER) of £44,964 per quality-adjusted life year (QALY) gained. The NICE DG states that this ICER is higher than what NICE would usually consider to represent a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained[2]). The NICE DG highlights that more up-to-date data were available from the 2022 data cut-off (DCO) of the INVICTUS trial[3] but these had not been included in the company's economic model. The Appraisal Committee requested that the company provide more information about this later DCO.

In December 2025, the company submitted its response to the NICE DG. The company's DG response includes a written response form[4] and an accompanying addendum.[5] The company's DG response form provides comments on a range of issues, including: statistical adjustment to remove the impact of intra-patient dose escalation (IPDE) to ripretinib 150mg BID and predictions of OS from INVICTUS;[3] the appropriateness and impact of using OS data from the the 2022 DCO of INVICTUS; clincial expectations of long-term OS for ripretinib; the appropriate cost-effectiveness threshold range for NICE decision-making and other factors including inequalities and uncaptured benefits which are not reflected in the modelled quality-adjusted life year (QALY) estimates. The main issues discussed by the company are summarised in Section 2 of this EAG addendum. The company's additional addendum describes the methods and results of additional analyses conducted using updated data from the 2022 DCO of INVICTUS, as well as further statistical analyses using the earlier 2021 DCO. Specifically, the company repeated all IPDE adjustments in the ripretinib arm using two-stage estimation (TSE) with and without re-censoring based on the 2022 DCO and re-fitted the standard parametric survival models to the adjusted OS data. In addition, it applied an alternative method for IPDE adjustment, namely TSE with inverse probability of censoring weights (TSE_{IPCW}), to both the 2021 and 2022 DCOs as additional scenario analyses and fitted standard parametric survival models to the adjusted OS data. The company's additional addendum also provides a summary of updated cost-effectiveness results generated using the company's economic model, including an increased Patient Access Scheme (PAS) discount of [redacted]. Whilst the company has conducted additional modelling analyses which include the

use of OS data from the 2022 DCO of INVICTUS, the company's DG response states that its base case approach remains unchanged; hence, the company's base case model adjusts for IPDE to ripreitnib 150mg BID using the TSE method (complex, generalised gamma model, without re-censoring) and applies the log-normal model for extrapolation of the IPDE-adjusted ripretinib data from the earlier 2021 DCO of INVICTUS.

The results of the company's base case model using the 2021 DCO of INVICTUS[3] and the updated PAS for ripretinib are presented in Table 1. The results of the EAG's and Appraisal Committee's preferred analysis (TSE adjustment using complex, generalised gamma model, with re-censoring; log-logistic model for extrapolation) are also presented in the table. Whilst the company's DG response includes additional statistical analyses to estimate the effect of ripretinib in patients who had received exactly three prior lines of therapy prior to enrolment in INVICTUS (i.e., the "true fourth-line" subgroup), the company has not presented ICERs for this subgroup. Based on the 2021 DCO of INVICTUS and the updated PAS, the company's deterministic base case ICER for the overall population is estimated to be £26,877 per QALY gained. The EAG's and the Appraisal Committee's preferred model (at the first Appraisal Committee Meeting [ACM1]) using the 2021 DCO suggests a higher ICER of £41,035 per QALY gained.

Table 1: Company's post-ACM1 base case model and EAG's preferred analysis at ACM1, 2021 DCO, includes updated PAS discount for ripretinib

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (DM= 1.7)
2021 DCO: Company's post-ACM1 base case model, TSE without re-censoring (complex, generalised gamma), log-normal model								
Ripretinib	2.90	[redacted]	[redacted]	2.59	[redacted]	[redacted]	£45,690	**£26,877**
BSC	0.31	[redacted]	[redacted]	-	-	-	-	
2021 DCO: EAG/Committee preferred model at ACM1, TSE with re-censoring (complex, generalised gamma), log-logistic model								
Ripretinib	1.79	[redacted]	[redacted]	1.47	[redacted]	[redacted]	£69,760	**£41,035**
BSC	0.31	[redacted]	[redacted]	-	-	-	-	-

ACM - Appraisal Committee Meeting; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; excl. - excluding; DM - decision modifier; DCO - data cut-off; BSC - best supportive care; EAG - External Assessment Group; TSE - two-stage estimation; IPCW - inverse probability of censoring weights

This EAG addendum provides a summary and critique of the company's DG response.[4] Section 2 summarises the main points raised in the company's DG response, together with comments from the EAG. Section 3 presents the results of additional analyses undertaken by the EAG using the updated economic model provided as part of the company's DG response, including the updated PAS for ripretinib.

2. Summary and critique of the main issues discussed in company's DG response

This section summarises the main issues discussed in the company's DG response form[4] together with comments from the EAG. The company's DG response includes discussion around several other issues including the quality of INVICTUS,[3] the sample size calculations and the potential impact of off-label therapies received prior to enrolment in INVICTUS on OS; for brevity, these issues are not discussed here.

Issue 1: Adjustment for IPDE, parametric survival model selection, and expectations of 10-year OS for ripretinib

NICE DG conclusions: The NICE DG[1] highlights that there is considerable uncertainty surrounding the impact of IPDE to ripretinib 150mg BID on OS estimates but concludes that the TSE including a more comprehensive set of covariates (i.e., the "complex model") was the most appropriate adjustment approach for taking account of the effect of post-progression dose escalation on OS in INVICTUS[3] (NICE DG, Section 3.7). The NICE DG highlights that the inclusion/exclusion of re-censoring when estimating counterfactual OS for the ripretinib group is a key driver of cost-effectiveness and states that the Appraisal Committee concluded that the EAG's preferred approach (i.e., TSE using complex generalised gamma model with re-censoring, and extrapolation using the log-logistic distribution) was more aligned with the empirical hazard and so was the most appropriate analysis (NICE DG, Section 3.8).

The NICE DG[1] also presents some information on clinical expectations of long-term OS for patients receiving ripretinib. The NICE DG states that the clinical experts who attended the company's 2024 advisory board meeting[6] provided estimates of 10-year OS for ripretinib ranging from 1-8% (the consensus estimate of [redacted] from the advisory board meeting could not be reported as it is considered confidential by the company). The DG also states that the two clinical experts who attended ACM1 suggested estimates of 10-year OS of 4-6% (although the NICE DG erroneously suggests that these estimates reflect OS under the current GIST treatment pathway without ripretinib, rather than a future pathway including ripretinib). The NICE DG states that the Appraisal Committee preferred to consider the extrapolation of OS for the INVICTUS trial population rather than expected OS for patients who would receive ripretinib as fourth-line therapy in clinical practice (who may be comparatively healthier and less heavily pre-treated given that the INVICTUS trial also included some patients with more than three prior lines of therapy). It also comments that the company's model appears to result in implausible survival estimates in the post-progression off-treatment health state for the ripretinib group, and notes that the EAG's analysis suggests a comparatively lower mean post-progression survival duration after discontinuing treatment with ripretinib (NICE DG, Section 3.9). The NICE DG states that the Appraisal Committee's preferred assumptions were in line with the EAG's preferred analysis (NICE DG, Section 3.15).

Company's DG response: The company's DG response[4] presents the following arguments:

- The company states that the EAG's preference for the TSE adjustment with re-censoring and the log-logistic model prioritises goodness-of-fit across the earlier portion of the hazard function and that this is not consistent with biological plausibility or expert opinion. The company's DG response suggests that the analysis which includes re-censoring removes substantial valid follow-up and results in very few patients being at risk at later time points. The company states that: *"This [re-censoring] is explicitly cautioned against in NICE TSD24 when extrapolating long-term outcomes. In contrast, the company's analyses of OS without re-censoring allows for the retention of full follow-up, are methodologically simpler, and produce clinically plausible long-term OS consistent with independent expert clinical opinion (4–6% survival following 10 years of ripretinib therapy)"* (Company's DG response,[4] page 3).
- The company argues that its preferred IPDE adjustment analysis (TSE without re-censoring) retains more follow-up information and is supported under NICE's technical guidance (the EAG presumes that the company is referring to NICE Technical Support Document [TSD] 24[7] although this is not explicitly stated in the company's DG response[4]). The company also states that its preference for TSE without re-censoring is based on its view that "*The more mature OS data available in the 2022 DCO and TSE-IPCW [two-stage estimation with inverse probability of censoring weights] analyses of OS in the 2021 DCO both indicate that the impact of informative bias is marginal. Therefore, the risks from potential informative bias in the two-stage estimation appear to be heavily outweighed by the loss of follow-up arising from re-censoring*." (Company's DG response,[4] page 3; note that the EAG considers the use of evidence from the 2021 versus 2022 DCOs as a separate issue and discusses this under Issue 2 below). The company states that the OS extrapolation without re-censoring was deemed clinically plausible and that it is consistent with clinician feedback obtained during ACM1 (10-year survival expectation of 4-6%).
- The company acknowledges the Appraisal Committee's observation that the company's base case model appears to provide an implausible survival prediction in the post-progression off-treatment state for ripretinib, but comments that it is possible that this is due to a "legacy effect" of ripretinb (this concept is not explained in the company's DG response but the EAG presumes that the company is referring to the possibility of a residual treatment effect for ripretinib which persists beyond discontinuation). It also states that the implausible post-progression off-treatment survival estimate may be a by-product of the partitioned survival modelling approach which includes the extrapolation of independent parametric survival models for OS and time to treatment discontinuation.
- The company argues that the provisional recommendations in the NICE DG *"appear to under-utilise expert clinician input"* – specifically, the company is referring to the EAG's and

Appraisal Committee's selection of a preferred analysis which gives a more pessimistic 10-year OS prediction for ripretinib compared to the estimate of 4-6% provided by the two clinical experts who attended ACM1. The company's DG response suggests that the plausibility of model-predicted OS should be based on the estimates provided by the clinical experts who attended ACM1.

EAG comments:

The EAG notes the following points:

- The company's DG response[4] seems to suggest that NICE TSD 24[7] supports analyses which exclude re-censoring and warns against analyses which include re-censoring. This is not an accurate interpretation of TSD 24 as it does not endorse one approach over the other. Rather, TSD 24 recommends that *"analyses should be performed with and without re-censoring, as this may give decision-makers a clearer idea of the range in which the true longer-term treatment effect lies."* In the EAG report[8] and the EAG's previous addendum (September 2025),[9] the EAG's preferred analysis included re-censoring in the TSE adjustment model and used the log-logistic model for extrapolation of the ripretinib OS data because this analysis provides a better fit to the hazard function and because it provides an estimate of 10-year OS which is similar to, albeit slightly lower than, the consensus estimate obtained from clinical experts who attended the company's 2024 advisory board meeting.[6] In keeping with the recommendations from TSD 24, the EAG's addendum included the results of analyses with and without re-censoring. The EAG notes however that none of the models without re-censoring provided predictions of 10-year OS which were similar to the consensus estimate.
- In the company's additional addendum which was provided alongside its DG response,[5] TSE_{IPCW} was performed as a scenario analysis in addition to the aforementiond TSE with and without re-censoring. Although NICE TSD 24[7] does not recommend TSE_{IPCW} as a routine analysis alongside TSE with and without re-censoring, it recognises this approach as a potential recent alternative to TSE with re-censoring to break the dependency between counterfactual survival times and switching times, while noting that TSE_{IPCW} is subject to the same limitations as IPCW (as a standalone method) more generally.[7] Latimer *et al.*[10] evaluated TSE_{IPCW} in simulation studies and found that it performed well, producing estimates between those obtained from TSE with and without re-censoring. Latimer *et al.* suggests that it may be useful to present TSE_{IPCW} alongside TSE with and without re-censoring to explore the sensitity in results. The EAG therefore considers the company's TSE_{IPCW} scenario analyses as an appropriate appraoch to explore, but notes its limitations and associated uncertainties. Specicially, the simulation study reported by Latimer *et al.* used a sample size of 500 patients, whereas INVICTUS[3] includes only 154 patients. IPCW is generally less stable with small sample sizes and a high proportion of censoring due to the potential for extreme weights;

however, as the weight distribution for the company's analysis was not reported, the EAG could not assess this further. The EAG notes that the company did not explore IPCW as a standalone method (without TSE) to adjust for IPDE in its original submission[11] due to the small sample size in INVICTUS; the EAG considers that the same concerns apply to TSE_{IPCW}, where potential instability due to small sample size remains an issue. Further, as highlighted in NICE TSD 24, TSE_{IPCW} also relies on the assumption that all relevant confounders related to censoring have been measured. The covariates used in the company's analysis were consistent with those in the TSE complex model, which the EAG considers reasonable; however, the assumption of no unmeasured confounders cannot be verified. In summary, both TSE with re-censoring and TSE_{IPCW} aim to break the dependence between counterfactual survival times and switching times, with TSE_{IPCW} theoretically preserving more long-term data than TSE with re-censoring. However, given its limitations, particularly the small sample size in INVICTUS, the EAG considers that the TSE_{IPCW} results should be interpreted with caution and, in line with the TSE_{IPCW} methodology paper,[10] used as an exploratory analysis alongside TSE with and without re-censoring to assess the sensitivity of the IPDE adjustment.

- Given the above considerations, the EAG does not fully agree with the company that retaining long-term information without adjusting for informative censoring (i.e., using TSE without re-censoring) should take precedence over attempts to adjust for informative censoring, although it recognises that inference from long-term data is important and therefore considers it reasonable to present TSE without re-censoring alongside TSE_{IPCW} and TSE with re-censoring. Further, the EAG disagrees with the company's view that the relatively similar results between TSE_{IPCW} and TSE without re-censoring (and between TSE with and without re-censoring, particularly using the 2022 DCO) guarantees that any bias arising due to informative censoring is small. In light of the recognised limitations of TSE_{IPCW} and the recommendations of Latimer *et al.*[10] the EAG considers that all three TSE approaches should be presented to assess the impact of the IPDE adjustment on the economic model results.
- The company's base case model suggests a mean post-progression survival duration after ripretinib discontinuation of [redacted] years. This model estimate appears to be implausible. As noted in Section 4.3.5 of the EAG report,[8] the EAG's clinical advisors stated that they would not expect a residual treatment effect on OS after patients have discontinued ripretinib. The EAG also considers that it is insufficient to simply dismiss this likely implausible model prediction as a by-product of the selected modelling approach.
- The EAG has summarised the estimates of 10-year OS for ripretinib available from clinical experts in Table 2. The company's DG response[4] states that its base case analysis is consistent with estimates of 10-year OS for ripretinib obtained from the clinical experts who attended NICE ACM1 (4-6%). However, the company's model predictions are more optimistic than

estimates of 10-year survival obtained from the majority of the clinical experts who provided numerical estimates of OS at the company's 2024 advisory board meeting[6] and the consensus estimate obtained from these experts (10-year survival expectation for ripretinib = [redacted]). The company's selected base case OS model is also more optimistic than the parametric survival models preferred by the EAG's clinical advisors which gave 10-year survival predictions for ripretinib of [redacted] and [redacted].

- The EAG does not believe that there is a strong rationale for placing more weight on the survival expectations provided by the two clinical experts who attended NICE ACM1 over those obtained from the seven clinical experts who attended company's 2024 advisory board meeting.[6] [redacted]
- The NICE DG[1] does not clearly state how considerations of clinical plausibility of model-predicted OS for ripretinib were used by the Appraisal Committee to select its preferred analysis. The EAG considers that this point could be clarified in the NICE Final Guidance. However, the EAG does not agree with the revised wording of DG Section 3.9 proposed by the company due to the reasons described in the bullet points above.

Table 2: Summary of clinical experts' expectations of 10-year OS for ripretinib

Source	Preferred estimate of 10-year OS for ripretinib	EAG comments
Company's 2024 advisory board meeting (7 clinical experts)	Expert 1: [redacted] is plausible Expert 2: [redacted] is an overestimate Expert 3: [redacted] Expert 4: [redacted] Expert 5: [redacted] Expert 6: [redacted] Expert 7: Not reported Consensus estimate: [redacted]	Estimates were provided for 6 of 7 attending clinical experts. Expert 1 stated that [redacted] OS at 10 years is plausible because treatments are improving and new options are being developed; however, this expert's view does not relate to expected OS if ripretinib was added to the current treatment pathway for GIST. The EAG therefore believes that this reported estimate should be interpreted with caution.
EAG's clinical advisors (2 clinical experts)	Experts 8 and 9: [redacted] to [redacted]	Based on parametric survival models fitted to IPDE-unadjusted OS data from INVICTUS
NICE Appraisal Committee 1 (2 clinical experts)	Experts 10 and 11: 4-6%	[redacted]

OS - overall survival; EAG - External Assessment Group; NICE - National Institute for Health and Care Excellence; GIST - gastrointestinal stromal tumor; IPDE - intra-patient dose escalation

Issue 2: Additional analyses including the 2022 DCO of INVICTUS

NICE DG conclusions: The NICE DG[1] highlights that data from the 2022 DCO of INVICTUS[3] were not included in the company's economic model. The NICE DG explains that whilst the company considered the updated data to be less robust than the 2021 DCO, the EAG considered that including this later DCO in the model could help to reduce uncertainty around long-term OS for ripretinib. The NICE DG states that the Appraisal Committee concluded that additional data from the 2022 DCO of INVICTUS would be helpful, or alternatively, the company should provide further justification regarding why the data should be assessed as poor quality (NICE DG, Section 3.10). The NICE DG also states that it would be useful if additional data included information on the numbers of people with disease progression including: (i) the number of people in the placebo arm of INVICTUS who had not progressed by the 2021 DCO, but may have progressed and with crossover status unknown by the 2022 DCO, and (ii) the number of people in the ripretinib arm of INVICTUS who had not progressed at the time of the 2021 DCO but may have progressed by the time of the 2022 DCO and whose dose escalation status was unknown (NICE DG, Section 3.10).

Company's DG response:

- The company's additional addendum[5] provided alongside its DG response includes updated IPDE adjustment analyses and survival extrapolations for the ripretinib arm. These included IPDE adjustment using TSE with and without re-censoring, as well as TSE_{IPCW}. For the former two TSE methods, the company performed TSE with both a simple model (including a less comprehensive covariate set) and complex model (including a more comprehensive covariate set), each fitted with Weibull, exponential, generalised gamma, Gompertz, log-logistic and log-normal distributions, consistent with the earlier analyses provided as part of its clarification response.[12] For TSE_{IPCW}, the company reported results using the complex generalised gamma model. Each TSE approach resulted in the generation of a counterfactual adjusted OS dataset for ripretinib, to which the company then fitted standard parametric survival models for extrapolation (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions). The company's addendum reports Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for each of these extrapolation models (based on the complex, generalised gamma TSE only) in the additional addendum (Tables 1-3).
- The company's additional addendum[5] presents the results of the updated economic model using data from the 2022 DCO as scenario analyses, retaining the same IPDE adjustment and extrapolation model specifications for the ripretinib arm as described in Issue 1. The only change was that all ripretinib analyses were re-run on the 2022 DCO.
- Despite having conducted updated analyses using data from the 2022 DCO, the company's DG response[4] states that its preference remains to use the 2021 DCO as the base case analysis, given that [redacted] The company also states that, because the 2022 DCO includes only OS and safety data (i.e., progression-free survival [PFS] and health-related quality of life [HRQoL] were not recorded), using a mixture of data cuts for different clinical effectiveness end points could introduce temporal heterogeneity across clinical and patient-relevant outcomes.
- Table 2 of the company's DG response[4] includes a summary of the number of progression events which occurred before and after the 2021 DCO in INVICTUS.[3] These figures were used to support the company's view that the 2021 and 2022 DCOs are similar and to justify retaining the 2021 DCO for its base case analysis (as discussed in the previous bullet point).

- The company's DG response[4] states that "[redacted], *the loss of information from re-censoring is still evident"*, and as previously noted in Issue 1, the company considers that the longer-term OS data from the 2022 DCO (showing relatively similar results across different TSE approaches) and the TSE_{IPCW} analyses applied to the 2021 DCO suggest that the impact of informative bias is small – therefore, it considers that the potential risks of informative censoring in the TSE appear to be outweighed by the loss of follow-up arising from re-censoring. The EAG interprets this as the company relying on the relative similarity of results across the different TSE approaches used to adjust for ripretinib IPDE in the 2022 DCO to suggest that informative censoring bias is not substantial, while still preferring the 2021 DCO for temporal alignment across outcomes. This leads the company to justify retaining the 2021 DCO analyses without re-censoring as the base case in its DG response[4] on the grounds that preserving as much long-term follow-up as possible in the 2021 DCO is more important than adjusting for informative censoring bias (whilst also electing not to use the longer-term data from the 2022 DCO).

EAG comments:

- The EAG agrees with the company's attempt to repeat all IPDE adjustment and survival extrapolation for the ripretinib arm using the 2022 DCO, alongside the additional scenario analysis using TSE_{IPCW}. As noted in Issue 1 of this addendum, the EAG considers TSE_{IPCW} to be an appropriate method to explore, but maintains that it should be presented alongside TSE with and without re-censoring to test whether the results are sensitive to the choice of IPDE adjustment method, in line with the TSE_{IPCW} methodology paper recommendations.[10] Further, the EAG does not agree that the smaller differences between the three TSE approaches in the 2022 DCO should be used to conclude that the magnitude of informative censoring bias is small or to support not addressing potential informative censoring bias in the 2021 DCO analyses. Each TSE approach has its own trade-offs[7, 10] and cannot be used in isolation to demonstrate that such bias is negligible, and it is problematic to use information from a later data cut to guide analyses of an earlier data cut with a different number of censoring events.
- Despite the absence of PFS and HRQoL data in the 2022 DCO, the EAG considers that, given the substantial uncertainty around IPDE adjustments for ripretinib and OS extrapolations, the 2022 DCO OS data provide important insights for informing long-term OS predictions by reducing reliance on shorter-term hazard-shape matching. In line with best practice,[7, 10] the EAG considers that TSE with and without re-censoring, together with TSE_{IPCW}, should be presented alongside each other using the 2022 DCO to better characterise the range of uncertainty for OS for decision-making.

- As the EAG prefers the use of the OS data from the 2022 DCO, it notes that the company did not provide AIC/BIC for selecting the model for TSE adjustments (i.e., the single model used to derive time ratios for IPDE adjustment for TSE with and without re-censoring, and TSE_{IPCW}), only for the extrapolation of counterfactual OS after adjustment with different TSE approaches. The EAG therefore questions whether the complex generalised gamma model remains the most appropriate choice for the TSE adjustment of data from the 2022 DCO.
- The EAG considers that regardless of which TSE adjustment approach and which DCO is preferred, it is important that the selected parametric survival model fitted to the adjusted data provides clinically plausible predictions of long-term OS for ripretinib. The additional statistical and economic analyses presented in the company's addendum to its DG response[5] are limited to the model choices applied to the 2021 DCO (both the model used to derive time ratios for IPDE adjustment and the survival extrapolation model), and graphical plots of the survival extrapolations have not been presented for any of the models fitted to data from the 2022 DCO. Section 3 of this EAG addendum contains the results of the company's updated economic model for all standard parametric survival models fitted to the TSE-adjusted OS data for ripretinib based on the 2022 and 2021 DCOs (TSE with re-censoring, TSE without re-censoring and using TSE_{IPCW}). In addition, survival model predictions and summary estimates of 10-year model-predicted OS and post-progression off-treatment survival time for ripretinib are provided for each analysis to aid committee deliberations regarding clinical plausibility.

Issue 3: Uncaptured benefits in the economic model

NICE DG conclusions: The NICE DG[1] states that there were no additional benefits of ripretinib that were not captured in the company's economic model (NICE DG, Section 3.17).

Company's DG response: The company's DG response[4] states that there are relevant uncaptured benefits including impacts on families and caregivers, including bereavement and the effects of maintaining HRQoL, and the value of hope. The company's DG response notes that these issues were mentioned in the company's submission (CS)[11] and that they were also discussed during the Appraisal Committee meeting. The company argues that *"these factors are relevant when judging the most plausible ICER and should be recognised as uncaptured benefits rather than ignored"* (Company's DG response, page 5).

EAG comments: The EAG agrees that potential caregiver effects and the value of hope are discussed in the CS;[11] however, the CS states that there are no data to inform these potential effects. The EAG notes that the NICE Reference Case[2] allows for the inclusion of caregiver effects, but the company has not attempted to quantify these impacts within its economic model. The value of hope resulting from access

to a health technology is not mentioned in the NICE Methods Manual and the EAG considers this to be of uncertain relevance for decision-making.

Issue 4: Inequalities

NICE DG conclusions: The NICE DG[1] states that the Appraisal Committee discussed potential equality issues raised by stakeholders but did not identify any equality issues, and no issues that could be addressed in a NICE technology appraisal (NICE DG, Section 3.16).

Company's DG response: The company's DG response[4] argues that the Appraisal Committee's failure to recommend ripretinib may result in indirect equity impacts including:

- Inequality in access by geography and centre, whereby only patients treated at specialist centres may be able to receive a similar therapy
- A disproportionate impact on a rare, high-need group resulting from restricting access to an additional active therapy
- Increased distress and reduced hope for patients with GIST and their familties.

EAG comments: As discussed in the EAG report,[8] the CS[13] (Table 1, page 17) states that *"there are no special considerations relating to issues of equity or equality."* The EAG is unsure whether the indirect effects described in the company's DG response[4] should be considered as relevant sources of inequality within a technology appraisal. The EAG also notes that the company has not attempted to quantify the impact of these potential indirect equity impacts, e.g., using distributional cost-effectiveness analysis;[14] hence, the magnitude of the inequality gap and the extent to which a positive recommendation for ripretinib could reduce this remains unclear.

Issue 5: Uncertainty surrounding the positioning of ripretinib in the NHS

NICE DG conclusions: The NICE DG[1] states that the anticipated use of ripretinib in clinical practice may differ from the experience of the INVICTUS trial[3] because in the trial people may have received treatment beyond progression before a fourth-line treatment, but if ripretinib was routinely available in clinical practice some people may switch to a fourth-line treatment immediately after progression.

Company's DG response: The company's DG response[4] states that if ripretinib was routinely available in NHS practice, patients would likely switch to it immediately after progression on third-line regorafenib and this is consistent with clinical guidelines published by the European Society for Medical Oncology (ESMO).[15] The company's DG response includes additional statistical analyses for the subgroup of patients who entered INVICTUS[3] after exactly three prior therapies versus the overall INVICTUS trial population and versus the subgroup of patients who received 4 or more previous

therapies and concludes that the effect of ripretinib in the target fourth-line population is likely to have been underestimated by the company's model.

EAG comments: The EAG believes that the uncertainty highlighted in the NICE DG[1] relates to the use of third-line regorafenib post-progression prior to switching to fourth-line ripretinib in clinical practice, rather than differences between the number of prior lines of therapy in INVICTUS versus the company's intended target fourth-line positioning of ripretinib, or whether the number of prior lines of therapy is a prognostic factor and/or treatment effect modifier. The EAG notes that the company has not conducted economic analyses of ripretinib versus best supportive care (BSC) in the fourth-line subgroup of INVICTUS and it is unclear whether the ICER would be markedly different from the intention-to-treat population.

Issue 6: Appropriate threshold for decision-making

NICE DG conclusions: The NICE DG[1] states that as a consequence of uncertainty resulting from the use of an earlier data-cut of INVICTUS,[3] uncertainty around the methods used to adjust for treatment switching and IPDE in the trial and uncertainty around expectations of long-term OS, the Appraisal Committee concluded that an acceptable ICER would be towards the lower end of the range that NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Company's DG response: The company's DG response[4] argues that further flexibility should be afforded to this appraisal. The company highlights that GIST is a rare disease, and also states that its analyses of the 2022 DCO of INVICTUS and the fourth-line subgroup analysis should be seen to alleviate uncertainty around the ICER. The company also draws reference to uncaptured benefits and inequalities (as described in Issues 3 and 4 above) when considering the relevant threshold for decision-making and requests greater acceptance of the remaining uncertainty for this appraisal. The company also refers to the forthcoming increase in NICE's cost-effectiveness threshold range and requests that these new thresholds are applied to ripretinib without pausing the appraisal.

EAG comments: The appropriate threshold for decision-making is a matter for the NICE Appraisal Committee to determine. However, the EAG notes that the NICE DG[1] states that the Appraisal Committee's preference for considering the lower end of the threshold range was partly driven by uncertainty resulting from the use of the earlier 2021 DCO of INVICTUS.[3] If the Appraisal Committee considers the updated economic analyses using the 2022 DCO of INVICTUS to be suitable for decision-making, it may also wish to revisit its preferred threshold for this appraisal.

3. Additional analyses conducted by the EAG

This section presents the results of additional economic analyses undertaken by the EAG using the company's model, including the updated PAS for ripretinib. ICERs are presented for all standard parametric models for OS in the ripretinib group across three scenarios: (i) TSE with re-censoring, (ii) TSE without re-censoring and (iii) TSE_{IPCW}. Results are presented for both the 2022 and 2021 DCOs.

Table 3 presents a summary of the model-predicted 10-year OS probability for ripretinib, the mean post-progression off-treatment survival duration and the ICERs for ripretinib versus BSC based on the company's updated model (including the updated PAS for ripretinib). Plots showing TSE-adjusted counterfactual OS and model-predicted OS for ripretinib based on the 2022 DCO are presented in Figure 1 (TSE with re-censoring), Figure 2 (TSE without re-censoring) and Figure 3 (TSE_{IPCW}). The equivalent plots based on the 2021 DCO are shown in Figure 4 (TSE with re-censoring), Figure 5 (TSE without re-censoring) and Figure 6 (TSE_{IPCW}).

Across the three sets of IPDE adjustment analyses applied to the 2022 DCO of INVICTUS,[3] the following parametric survival models for extrapolation give predicted 10-year OS probabilities for ripretinib which are closest to the consensus estimate of [redacted] from the company's advisory board meeting:

- TSE with re-censoring – log-normal model, 10-year OS = [redacted]; ICER = £33,562 per QALY gained
- TSE without re-censoring – generalised gamma model, 10-year OS = [redacted]; ICER = £31,437 per QALY gained
- TSE_{IPCW} – generalised gamma model, 10-year OS = [redacted]; ICER = £32,379 per QALY gained.

The EAG does not believe that any of these models can be ruled out.

When OS data from the earlier 2021 DCO of INVICTUS are included in the economic model,[3] the only analyses which provide predictions of 10-year OS which are similar to the consensus estimate of [redacted] are the TSE with-recensoring, log-normal and log-logistic models:

- TSE with re-censoring – log-normal model, 10-year OS = [redacted]; ICER = £37,850 per QALY gained; log-normal model, 10-year OS = [redacted]; ICER = £41,035 per QALY gained.

The EAG believes that the analyses based on the 2022 DCO should be considered to be the most relevant for decision-making. As such, the EAG's preferred ICER range is £31,437 to £33,562 per QALY gained.

Table 3: Summary of model-predicted 10-year OS, post-progression off-treatment survival time and cost-effectiveness results for TSE-adjusted models, includes new ripretinib PAS

Scenario	10-year OS probability for ripretinib	Mean post-progression off-treatment OS for ripretinib	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (excl. DM)	ICER (incl. DM =1.7)
TSE with re-censoring, DCO 2022							
Exponential	[redacted]	[redacted]	1.30	[redacted]	[redacted]	[redacted]	**£41,115**
Weibull	[redacted]	[redacted]	1.06	[redacted]	[redacted]	[redacted]	**£48,253**
Gompertz	[redacted]	[redacted]	1.02	[redacted]	[redacted]	[redacted]	**£49,780**
Log-normal*	[redacted]	[redacted]	1.66	[redacted]	[redacted]	[redacted]	**£33,563**
Log-logistic	[redacted]	[redacted]	1.64	[redacted]	[redacted]	[redacted]	**£34,026**
Gen. gamma	[redacted]	[redacted]	1.31	[redacted]	[redacted]	[redacted]	**£40,840**
TSE without re-censoring, DCO 2022							
Exponential	[redacted]	[redacted]	1.47	[redacted]	[redacted]	[redacted]	**£37,008**
Weibull	[redacted]	[redacted]	1.45	[redacted]	[redacted]	[redacted]	**£37,492**
Gompertz	[redacted]	[redacted]	2.04	[redacted]	[redacted]	[redacted]	**£28,408**
Log-normal	[redacted]	[redacted]	1.80	[redacted]	[redacted]	[redacted]	**£31,371**
Log-logistic	[redacted]	[redacted]	1.82	[redacted]	[redacted]	[redacted]	**£31,136**
Gen. gamma*	[redacted]	[redacted]	1.80	[redacted]	[redacted]	[redacted]	**£31,437**
TSE_{IPCW}, DCO 2022							
Exponential	[redacted]	[redacted]	1.47	[redacted]	[redacted]	[redacted]	**£36,973**
Weibull	[redacted]	[redacted]	1.46	[redacted]	[redacted]	[redacted]	**£37,099**
Gompertz	[redacted]	[redacted]	2.32	[redacted]	[redacted]	[redacted]	**£25,711**
Log-normal	[redacted]	[redacted]	1.78	[redacted]	[redacted]	[redacted]	**£31,728**
Log-logistic	[redacted]	[redacted]	1.88	[redacted]	[redacted]	[redacted]	**£30,409**
Gen. gamma*	[redacted]	[redacted]	1.73	[redacted]	[redacted]	[redacted]	**£32,379**
TSE with re-censoring, DCO 2021							
Exponential	[redacted]	[redacted]	1.20	[redacted]	[redacted]	[redacted]	**£43,898**
Weibull	[redacted]	[redacted]	0.88	[redacted]	[redacted]	[redacted]	**£56,197**
Gompertz	[redacted]	[redacted]	0.87	[redacted]	[redacted]	[redacted]	**£57,116**
Log-normal*	[redacted]	[redacted]	1.44	[redacted]	[redacted]	[redacted]	**£37,850**
Log-logistic	[redacted]	[redacted]	1.31	[redacted]	[redacted]	[redacted]	**£41,035**
Gen. gamma	[redacted]	[redacted]	0.88	[redacted]	[redacted]	[redacted]	**£56,375**
TSE without re-censoring, DCO 2021							
Exponential*	[redacted]	[redacted]	1.56	[redacted]	[redacted]	[redacted]	**£35,136**
Weibull	[redacted]	[redacted]	1.54	[redacted]	[redacted]	[redacted]	**£35,503**
Gompertz	[redacted]	[redacted]	3.78	[redacted]	[redacted]	[redacted]	**£17,346**
Log-normal	[redacted]	[redacted]	2.17	[redacted]	[redacted]	[redacted]	**£26,877**
Log-logistic	[redacted]	[redacted]	2.15	[redacted]	[redacted]	[redacted]	**£27,210**
Gen. gamma	[redacted]	[redacted]	2.54	[redacted]	[redacted]	[redacted]	**£23,709**
TSE_{IPCW}, DCO 2021							
Exponential	[redacted]	[redacted]	1.44	[redacted]	[redacted]	[redacted]	**£37,649**
Weibull*	[redacted]	[redacted]	1.47	[redacted]	[redacted]	[redacted]	**£37,074**
Gompertz	[redacted]	[redacted]	3.64	[redacted]	[redacted]	[redacted]	**£17,915**
Log-normal	[redacted]	[redacted]	1.91	[redacted]	[redacted]	[redacted]	**£29,881**
Log-logistic	[redacted]	[redacted]	1.97	[redacted]	[redacted]	[redacted]	**£29,282**
Gen. gamma	[redacted]	[redacted]	2.32	[redacted]	[redacted]	[redacted]	**£25,540**

EAG - External Assessment Group; IPDE - intra-patient dose escalation; OS - overall survival; TSE - two-stage estimation; IPCW - inverse probability of censoring weights; PAS - Patient Access Scheme; LYG - life year gained; QALY - quality-adjusted life year gained; ICER - incremental cost-effectiveness ratio; DM - decision modifier; DCO - data cut-off

** Model estimate closest to conensus estimate for 10-year OS on ripretinib of* [redacted]

Figure 1: Kaplan-Meier plot of ripretinib OS adjusted for IPDE (TSE with re-censoring) and survival model predictions, DCO 2022 (drawn by the EAG)

Figure 2: Kaplan-Meier plot of ripretinib OS adjusted for IPDE (TSE without re-censoring) and survival model predictions, DCO 2022 (drawn by the EAG)

Figure 3: Kaplan-Meier plot of ripretinib OS adjusted for IPDE (TSE_{IPCW}) and survival model predictions, DCO 2022 (drawn by the EAG)

Figure 4: Kaplan-Meier plot of ripretinib OS adjusted for IPDE (TSE with re-censoring) and survival model predictions, DCO 2021 (drawn by the EAG)

Figure 5: Kaplan-Meier plot of ripretinib OS adjusted for IPDE (TSE without re-censoring) and survival model predictions, DCO 2021 (drawn by the EAG)

Figure 6: Kaplan-Meier plot of ripretinib OS adjusted for IPDE (TSE_{IPCW}) and survival model predictions, DCO 2021 (drawn by the EAG)

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