NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more kinase inhibitors

Recommendation

1.1 Ripretinib can be used, within its marketing authorisation, as an option to treat advanced gastrointestinal stromal tumours (GISTs) in adults after 3 or more kinase inhibitors, including imatinib. Ripretinib can only be used if the company provides it according to the commercial arrangement.

What this means in practice

Ripretinib must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. Ripretinib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that ripretinib provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made this recommendation

Usual treatment for advanced GISTs, after the tyrosine kinase inhibitors imatinib, sunitinib and regorafenib, is best supportive care.

Clinical trial evidence shows that ripretinib plus best supportive care increases how long people have before their cancer gets worse and how long they live compared with placebo plus best supportive care.

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There are uncertainties in the economic model, including:

- how it adjusted for people in the trial who had a higher dosage of ripretinib than they would have in the NHS
- a lack of evidence on how long people are likely to live, especially after stopping ripretinib.

But when considering the condition's severity, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, ripretinib can be used.

2 Information about ripretinib

Marketing authorisation indication

2.1 Ripretinib (Qinlock, Deciphera Pharmaceuticals) is indicated for 'the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ripretinib.

Price

2.3 The list price of ripretinib is £18,400 per 30-day supply (excluding VAT; company submission). This is based on a 150-mg dose once daily (3 x 50-mg tablets).

2.4 The company has a commercial arrangement. This makes ripretinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Deciphera Pharmaceuticals will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Deciphera Pharmaceuticals, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition and treatment pathway

Gastrointestinal stromal tumour

3.1 Gastrointestinal stromal tumour (GIST) is a rare cancer that affects life expectancy and quality of life. Metastatic or unresectable GIST is treated with tyrosine kinase inhibitors (TKIs). The patient group explained that side effects of treatment can include nausea, diarrhoea, skin rashes and sore hands and feet. TKIs can also damage kidney and liver function. TKIs are used in the following sequence:

- imatinib at first line for unresectable or metastatic GIST (see NICE's technology appraisal guidance on imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours)
- sunitinib at second line if GIST progresses or the person cannot tolerate imatinib (see NICE's technology appraisal guidance on sunitinib for the treatment of gastrointestinal stromal tumours)
- regorafenib at third line if there is further progression or GIST does not respond to imatinib and sunitinib (see NICE's technology appraisal guidance on regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours, from here TA488).

If the cancer progresses or people cannot tolerate the available

options, the only fourth-line treatment option is best supportive care. Because of the limited treatment options, each option is used until maximum clinical benefit is gained before moving to the next line of treatment. A patient expert noted that these treatments can be effective for more common GIST mutations. But treatment options are limited when GIST no longer responds to current treatments. A clinical expert noted that treatment resistance can happen when secondary mutations, such as exon 17 and exon 18, develop after treatment with targeted TKIs. Third-line treatment with regorafenib can be continued after disease progression. But, when treatment stops working because the GIST has mutated, the only option is best supportive care or, if available, treatment in a clinical trial. A patient expert explained that this can be difficult to cope with mentally because clinical trials have uncertain outcomes. A clinical expert explained that, because sunitinib and regorafenib have cardiovascular side effects, people with existing cardiovascular disease can find them difficult to tolerate. Although treatments can be tried again, this is not usually effective. The clinical experts stated that the cancer usually progresses within weeks of starting the retreatment, especially if the person has an exon 17 or exon 18 mutation. 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. This is because of:

- earlier diagnosis
- increasing knowledge about available treatments, and
- improvements in managing treatment side effects.

The committee concluded that there is an unmet need for an effective treatment option after imatinib, sunitinib and regorafenib, especially for advanced GIST with exon 17 or exon 18 mutations.

Ripretinib dosing

3.2 Ripretinib is a TKI that slows tumour cell growth by attaching to 2 key receptors:

- KIT and proto-oncogene receptor tyrosine kinase
- platelet-derived growth factor receptor alpha (PDGFRA).

The patient experts stated that the side effects of ripretinib are manageable compared with the side effects from some of the other TKIs. They also highlighted that people have reported having a better quality of life with ripretinib compared with regorafenib. The clinical experts stated that there appeared to be no dose-limiting toxicity associated with ripretinib. This is unlike with imatinib, with which an increased dose provides extra benefits but is more toxic. This is because small changes in the serum concentration of imatinib can have negative adverse effects. The clinical experts also noted that healthcare professionals would like the option to consider a twice-daily dosage of ripretinib to maximise treatment options. The committee concluded that twice-daily dosage was not in the marketing authorisation for ripretinib, so only the once-daily dosage could be appraised in this evaluation. But it acknowledged that escalating to a twice-daily dosage was something that healthcare professionals would like to offer in practice.

Clinical effectiveness

INVICTUS trial

3.3 The clinical-effectiveness evidence for ripretinib came from INVICTUS, an international, multicentre, randomised, double-blind, placebo-controlled phase 3 trial. It compared the efficacy of 150 mg of ripretinib once daily plus best supportive care (n=85; ripretinib group) and placebo plus best supportive care (n=44; placebo group). The trial included adults who had:

- a histologically confirmed diagnosis of GIST

- at least 1 measurable lesion
- a European Oncology Group (ECOG) performance status of 0 to 2, and
- tried imatinib, sunitinib, and regorafenib and either:
  - their cancer progressed, or
  - they did not tolerate the treatment despite dose modifications.

Treatment with ripretinib was continued until disease progression or unacceptable toxicity. At disease progression, people having 150 mg of ripretinib once daily could:

- continue having their current dosage
- increase the dosage to 150 mg twice daily, or
- stop having ripretinib.

If their cancer got worse, people having placebo could cross over to 150 mg of ripretinib once daily or stop taking part in the study. If they stayed in the study and had a second disease progression after crossing over to ripretinib, they could continue at their current dosage, increase it to twice daily or stop having ripretinib.

Clinical-effectiveness results

3.4 At the May 2019 data cut, the median progression-free survival (PFS) in the intention-to-treat population was 6.3 months for the ripretinib group and 1.0 months for the placebo group. PFS was statistically significantly longer in the ripretinib group than in the placebo group (hazard ratio 0.15, 95% confidence interval [CI] 0.09 to 0.25, $p<0.0001$). A similar PFS was reported in March 2020 and January 2021. PFS was also assessed for the 29 people randomised to placebo who crossed over to 150 mg of ripretinib once daily. The unadjusted analyses showed that the median PFS was 4.6 months in this group. At the August 2020 data cut, unadjusted analyses showed that PFS for the 43 people who increased their dosage to 150 mg of ripretinib twice daily was 3.7 months after the dosage increase.

The unadjusted analyses in the intention-to-treat population showed that overall survival (OS) was 15.1 months for the ripretinib group compared with 6.6 months for the placebo group. The hazard ratio for ripretinib compared with placebo was 0.36 (95% CI 0.21 to 0.62, p value not reported). Median OS in the 29 people who crossed over from placebo to ripretinib was 11.6 months compared with 1.8 months in people who did not cross over. The unadjusted data showed that, at the August 2020 data cut, the median OS for the 43 people who increased their dosage to twice daily was 18.4 months. For the people who did not increase their dosage, it was 14.2 months. In response to clarification, the company had provided summary OS data for the latest data cut (May 2022). But the company considered the hazard ratio confidential, so it cannot be presented here. The committee noted that at first disease progression:

- 51% (43 out of 85) of people originally randomised to ripretinib once daily had increased their dosage to twice daily
- 66% (29 out of 44) of people randomised to placebo crossed over to have ripretinib once daily.

The company stated that it allowed people whose cancer had progressed to increase dosage because there were no treatment options at this point in the pathway (see section 3.1). The committee thought that the extent of OS benefit was very uncertain because of the:

- small number of people taking part in the trial
- large number of people who had either crossed over or increased their dosage while having ripretinib.

But the committee concluded that these results showed better PFS and OS for people having ripretinib plus best supportive care compared with people having placebo plus best supportive care.

Adjusting OS for dose escalation after disease progression

3.5 The committee recalled that, at the August 2020 INVICTUS data cut, 51% of people randomised to 150 mg of ripretinib increased their dosage from once to twice a day after disease progression. The company noted that its unadjusted analyses of dose escalation (see section 3.4) were uncertain. This was because it had not adjusted for possible predictive or prognostic factors that could have biased results. The company's submission said that, at the time of progression, 51% of people who increased their dosage had an ECOG score of 0. This was compared with 18% who stayed on a once-daily dosage, who had an ECOG score of 0. It noted that a lower ECOG score had been associated with longer survival in people with advanced GIST. So, the imbalance in ECOG status could have contributed to a perceived benefit in people having twice-daily dosing compared with those who did not.

Because the impact of dose escalation on OS estimates was unclear, the company carried out a series of post-hoc analyses. The analyses assessed whether increasing the dose of ripretinib after progression from once to twice daily would affect OS. Each of the analyses gave different results, which could have been subject to bias, and there was no clear trend in the data. The committee recalled that only the once-daily dosage could be evaluated in this evaluation. But it was also aware that some people in INVICTUS could move from a once daily to a twice-daily dose of ripretinib, which could have affected their OS. So, the committee concluded that the OS should be adjusted to account for some people having had twice-daily dosing in INVICTUS (see section 3.8).

Company's modelling approach

Economic model

3.6 The company presented a partitioned survival approach with 4 health states:

- progression-free
- progressed disease (on treatment with ripretinib)
- progressed disease (off treatment with ripretinib, that is, best supportive care)
- death.

This approach was used to capture the effects of continued treatment after disease progression by dividing the progressed-disease health state into on treatment and off treatment. The committee concluded that the model was appropriate for decision making.

Including a later data cut of INVICTUS OS data in the economic model

3.7 The company's economic model at the first committee meeting was informed by the January 2021 data cut of INVICTUS. But there was a later data cut of INVICTUS from May 2022. The company explained that the original model was built before the 2022 data became available. It also said that the 2022 data was less robust than the 2021 data. So, the company argued that including the 2022 data for OS in the economic model would cause heterogenous clinical inputs and increase the risk of bias created by collecting data from an open-label setting. Although the company had provided OS estimates for the 2022 data cut, it had not done any analyses to incorporate the data into the model. The company explained that it had considered the feasibility and impact of the final OS data from 2022. The company reiterated that it had made a proactive decision not to include the additional 16 months of OS data in the model. This was because it thought that the 2021 data was sufficiently mature and that the hazard ratio for OS was similar, with few people at risk in the additional 16 months. The EAG noted that the 2022 data could provide additional information to inform long-term OS predictions and provide more reliable estimates. It thought that longer-term data would help to reduce the impact of information loss caused by recensoring (see section 3.9). 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 people who did not. But it noted that this would have taken time and been expensive to do. It thought that, for its decision making, it would be helpful to have the additional data from the May 2022 data cut of INVICTUS analysed and incorporated in the model. Otherwise, the committee would need sufficient justification from the company explaining why the data was assessed as poor quality.

In response to the draft guidance consultation, the company provided additional 2-stage adjustment analyses using the 2022 data cut of INVICTUS (see section 3.9). But the company preferred to use the 2021 data cut in its base case, maintaining that using 2022 data gave heterogenous clinical inputs in the economic model. This is because the prespecified end-of-study analyses only included OS and safety outcomes. PFS outcomes and health-related quality-of-life data were not included after the 2021 data cut, and assumptions were needed regarding treatment switching and progression beyond that point. The EAG said that the use of 2022 data reduced reliance on the short-term OS hazard ratio. So, it preferred to use the 2022 data. The committee thought that the 2021 data analysis being prespecified was not a strong argument against using the available 2022 data. This was especially when long-term OS relied on an extrapolation that is beyond the observed data. It also heard from the company that most progression and treatment switching had already occurred in the 2021 data. So, it considered that using 2022 data did not introduce substantial additional methodological uncertainty. The committee acknowledged that additional analyses using the 2022 data cut addressed some uncertainties because it used longer-term OS data from INVICTUS. The committee concluded that May 2022 INVICTUS data helped reduce uncertainty in long-term OS and was more appropriate to inform the economic model.

Adjusting for increasing the dosage

3.8 Clinical-effectiveness parameters in the company's model were based on INVICTUS data from January 2021, which was extrapolated to inform health-state occupancy. When their cancer progressed, people in INVICTUS could either stay on 150 mg of ripretinib once daily or increase to twice daily (see section 3.5). The company's base case had originally adjusted the data to account for people crossing over from placebo to ripretinib. But it had not adjusted the data to account for the effects of the unlicensed twice-daily dosing on OS estimates in this base case. The company had considered adjusting OS data for increasing dosage in the ripretinib group in its scenario analyses. The company did this by using a simple model adjusting only for time to progression. It also used a complex model adjusting for time to progression, ECOG performance status at progression, Euroqol 5-Dimensions visual analogue scale (EQ-VAS) score at progression, and baseline age. The EAG thought that the company's scenario analyses that applied the 2-stage adjustment were the only appropriate analyses supporting a causal interpretation of the effect of increasing dosage. For this analysis, the company had noted that the generalised gamma distribution for the complex model was the best fitting adjustment. The company revised its base case before the first committee meeting to include the 2-stage adjustment. This was applied using a complex model (and the generalised gamma distribution to identify the time ratio). The complex model used a range of parametric distributions to get time ratios. The first stage estimated the effect of people switching to a twice-daily dosage rather than continuing with a once-daily dosage. The second stage applied these time ratios to estimate counterfactual OS, as though treatment had continued without increasing the dosage. The EAG agreed that the complex model using the generalised gamma distribution had the best statistical fit for estimating counterfactual OS. The committee recognised there was large uncertainty about the impact of increasing dosage on OS estimates. But it concluded

that the complex 2-stage estimation was the most appropriate adjustment for taking account of the effect of increasing dosage on OS in INVICTUS.

Recensoring data

3.9 Because the INVICTUS data had included censoring for people who had increased their dosage, recensoring could be used to adjust the data for people who increased their dosage and for people who did not. NICE Decision and Technical Support Unit's technical support document 24 (TSD 24) recommends presenting results with and without recensoring for 2-stage adjustment analysis. But the company said that applying recensoring could introduce uncertainty to the long-term OS extrapolations. It said that this is because survival follow up for people having ripretinib was much shorter with recensoring. Also, there was a reduction in the number of people at risk compared with not including recensoring. TSD 24 explains that recensoring aims to break the dependence between treatment, counterfactual censoring time and prognosis, which may bias the adjusted data. Parametric survival models were fitted to each counterfactual dataset for extrapolation. The company preferred the log-normal model, without recensoring. The EAG noted that applying the adjustment for increasing the dosage with or without recensoring was the biggest driver of the cost-effectiveness estimates. The EAG noted that none of the extrapolated models that were fitted without recensoring provided a satisfactory fit to capture the timing of the first hazard increase in the 2-stage adjusted data. But fitting the log-logistic model with recensoring more closely aligned with the smoothed empirical hazard. So, it preferred to extrapolate the counterfactual OS in this way. The committee thought there was considerable uncertainty in interpreting the OS because of the number of data adjustments needed.

In response to the draft guidance consultation, the company presented additional 2-stage adjusted analyses with and without recensoring based on the 2022 INVICTUS data. It also provided additional analyses using 2-stage adjusted data using inverse probability of censoring weights

(IPCW) to both the 2021 and 2022 INVICTUS data. The company highlighted that the more mature OS data available in the 2022 data cut and the IPCW analyses of OS in the 2021 data cut showed that the impact of informative bias was marginal and outweighed by the loss of follow up from recensoring. So, it continued to prefer the 2-stage adjustment without recensoring in its base case. The EAG said that TSD 24 does not recommend 2-stage adjustment with IPCW as a routine analysis alongside 2-stage adjustment with and without recensoring. But it acknowledged that TSD 24 does recognise 2-stage adjustment with IPCW as a potential alternative to 2-stage adjustment with recensoring to break the dependency between counterfactual survival times and switching times. The EAG also thought that the relatively similar results between 2-stage adjustment with IPCW and without recensoring did not guarantee that any bias arising because of informative censoring was small. So, the EAG presented economic analyses using all 3 2-stage adjustment approaches. The committee acknowledged that the additional adjustment analyses provided by the company were useful. But it remained cautious over choosing one adjustment approach over another because of the limitations associated with all 3 adjustment approaches. The committee concluded that all 3 2-stage adjustments should be considered in the economic model.

Plausibility of OS predictions at the first committee meeting

3.10 The company had sought clinical opinion, through an advisory board with 7 clinical experts, on the plausibility and validity of the survival probability produced by the OS modelling it used in its economic model. In its submission, it stated that published estimates of the 10-year survival rates for people starting first and second lines of treatment ranged from 10% to 23%. But it noted that, after progressing on imatinib, the cancer can progress quickly. Treatment with sunitinib and regorafenib can only provide 6 to 9 months of benefit before the cancer gets worse. For people who have second-line sunitinib, 10-year survival is about 10%. Estimates from the company's advisory board for the projected 10-year survival for

ripretinib ranged from 1% to 8%. The consensus estimate of the company's advisory board is considered by the company as confidential, so cannot be presented here. The company's modelling approach (without recensoring and log-normal extrapolation) resulted in a 10-year OS that was higher than the advisory board consensus estimate. The EAG said that its OS modelling had better external validity. This was because its extrapolation (recensoring and using the log-logistic model) projected a 10-year survival that was closer to the company's advisory board consensus estimate. The clinical experts at the first committee meeting said that when ripretinib is given at fourth line and onwards, 4% to 6% OS after 10 years is plausible. 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 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. These estimates are considered confidential by the company and cannot be reported here. The clinical expert responded that, because people in INVICTUS were having treatment abroad, they may have had off-label treatment with other drugs, such as immunotherapies. This may have had a stabilising effect. The EAG stated that its clinical advisers had said they would expect no residual effect after stopping treatment. Also, the EAG's preferred analysis (using recensoring) showed less modelled survival gain after progression compared with the company's modelled survival (without recensoring). The committee recognised that people in current clinical practice who have treatment at this point in the pathway may be different to the people in the trial. But the OS estimates in the economic model were based on the population in INVICTUS, in which people had exhausted all other options and their disease had progressed after having regorafenib. It highlighted that the severity decision modifier (and other model inputs) were based on the INVICTUS population. This may be a sicker population than would be expected to have ripretinib in NHS clinical practice. The committee

acknowledged the uncertainty in 10-year OS estimates generated through different clinical expectations of survival. It noted that the 10-year OS estimates using the EAG's approach were closest to the company's advisory board consensus estimate.

Plausibility of OS predictions at the second committee meeting

3.11 In response to the draft guidance consultation, the company said that the committee's preferred modelling approach at the first committee meeting resulted in a more pessimistic 10-year OS. It explained that this was not aligned with the clinical experts' opinion at that meeting. It also said that the implausible OS estimates in the ripretinib arm in the post-progression off-treatment state may be possible because of a legacy effect with ripretinib. At the second committee meeting, the committee questioned the clinical rationale of a potential legacy effect with TKIs, which resulted in a large post-progression off-treatment benefit in the ripretinib arm. The clinical experts at that meeting said that this may be because of ripretinib's dual-switch mechanism of action, which is different to the ATP binding pocket mechanism of action of other available TKIs for GIST. This action results in more efficient targeting of secondary mutations compared with sunitinib and regorafenib. But the committee thought that this did not fully explain the large post-progression off-treatment survival benefit when the cancer had progressed. One clinical expert further explained that ripretinib is so well tolerated that some people remain fit enough to have surgery, ablation or radiotherapy after stopping ripretinib following disease progression. The committee was aware that ripretinib is positioned as last-line treatment for GIST in this appraisal, so the analyses assume there are no subsequent treatments available. But the committee said that these post-progression treatments should be considered in both the ripretinib and the best supportive care arm. It also said that the costs of these treatments should be included in both arms in the economic modelling. The committee recalled the uncertainty from different clinical expectations of long-term OS. It preferred to use the company's advisory board consensus estimate as the most plausible 10-year OS estimate.

This was because it used formal elicitation methods and input from a larger number of clinical experts. The company said that the clinical experts at the first committee meeting had direct experience of using ripretinib in their clinical practice. The company also said that not all the clinical experts at the advisory board, and none of the EAG's clinical advisers, had experience with ripretinib. But the company did not confirm how many clinical experts at the advisory board had experience with ripretinib or whether any of these experts' estimates were double counted. The committee said that it still preferred the company's advisory board consensus estimate. This was because the company had invited clinical experts who had relevant experience with GIST, including using ripretinib, in their clinical practice. The exact details from the company's advisory board are confidential and cannot be reported here. The committee considered the company's base-case model and the EAG's updated approach using 2022 INVICTUS data with all 2-stage adjustment methods. It noted that the 10-year OS estimates from these were higher than the company's advisory board consensus estimate and the EAG's clinical adviser estimate. But the EAG's 10-year OS estimates were closest to the advisory board's consensus estimate, so were likely more plausible. The committee concluded that the EAG's range of 10-year OS estimates using all 2-stage adjustments were plausible.

Source of utility values

3.12 In NICE's technology appraisal guidance on ripretinib for treating advanced GIST after 3 or more treatments (from here TA881) the company's base-case analysis used utility values from INVICTUS as a single data source. But the EAG had preferred to use a utility value from the GRID trial that was used in TA488. The EAG explained that the company had updated its model structure for this evaluation (since TA881) to include continued treatment after disease progression (see section 3.6). So, the EAG's original concern about applying the utility sources from GRID was no longer relevant. In this evaluation, both the company and the EAG had used the utility values from INVICTUS in their

base cases. The committee noted that including utility values from GRID had minimal impact on the cost-effectiveness estimates. It concluded that using utility values from data collected from INVICTUS was appropriate.

Severity

3.13 The committee considered the severity of the condition (the future health lost by people living with the condition having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs), called a severity modifier, if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company and the EAG agreed that a decision modifier of 1.7 was appropriate. This was based on the characteristics of people in INVICTUS and the mean estimate of QALYs for people in the best supportive care arm of the economic model. The committee noted that the INVICTUS trial concluded in 2022. It recalled that the clinical experts had explained that survival outcomes for people needing a fourth-line treatment for GIST in clinical practice have improved (see section 3.1 and section 3.10). So, ripretinib may be used differently in clinical practice to how it was used in the trial because:

- regorafenib may not be used if testing has suggested that there is a mutation that means it will not be effective
- in INVICTUS, people may have had treatment beyond progression before a fourth-line treatment, but if ripretinib were to be 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. The economic model inputs were based on INVICTUS data, and the assessment of severity was based on the INVICTUS population. In the absence of other available information,

the committee concluded that it could accept that the severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.14 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty around the:

- impact on the OS from adjusting the trial data for crossover and increased doses (see section 3.8 and section 3.9)
- expected size of the 10-year OS benefit caused by uncertainties in the adjustments to the trial data, improvements in the treatment pathway and large post-progression off-treatment survival (see section 3.10 and section 3.11).

The committee noted that these issues were big drivers in the cost-effectiveness estimates. But the committee recognised the challenges of producing robust evidence in a small population. It also decided that the introduction of additional analyses using 2022 data from INVICTUS had reduced some uncertainty. So, the committee concluded that an acceptable ICER would be towards the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.15 The company's base-case analysis used the January 2021 INVICTUS data and the 2-stage complex model with generalised gamma, but without recensoring, applying the log-normal extrapolation. The company's deterministic base-case analysis produced an ICER of £24,937 per QALY gained. The EAG used the May 2022 INVICTUS data and 2-stage complex model with generalised gamma. But it presented a range of deterministic ICERs using these 2-stage adjustments:

- £31,085 per QALY gained with recensoring, applying the log-normal extrapolation
- £29,130 per QALY gained without recensoring, applying the generalised gamma extrapolation
- £29,995 per QALY gained with IPCW, applying the generalised gamma extrapolation.

Both the company's base case and the EAG's range of ICERs applied a QALY weighting of 1.7.

Committee's preferred assumptions

3.16 The committee's preferred assumptions included:

- using May 2022 INVICTUS data to inform the economic model (see section 3.7)
- using a 2-stage complex model with generalised gamma to adjust for the effect of increasing ripretinib dosage on OS in INVICTUS (see section 3.8)
- considering the 2-stage adjustment with and without recensoring, and IPCW to assess the impact on the cost-effectiveness results (see section 3.9)
- that the EAG's range of 10-year OS estimates using all 2-stage adjustments are plausible (see section 3.11)

- using utility values from data collected from INVICTUS (see section 3.12).

When selecting a cost-effectiveness estimate for decision making, it considered an ICER around the midpoint of the range using all 2-stage adjustment methods. Taking into account the committee's preferred assumptions, an ICER around the midpoint of the range of ICERs was considered an acceptable use of NHS resources.

Other factors

Equality

3.17 The committee discussed potential equality issues raised by stakeholders but agreed that these were either not equality issues or could not be addressed in a NICE technology evaluation. The committee did not identify any other equality issues that could be addressed in a NICE technology evaluation.

Uncaptured benefits

3.18 The committee considered whether there were any uncaptured benefits of ripretinib. It did not identify any, and the company did not highlight any additional benefits that were not captured in the economic modelling. So, the committee concluded that all additional benefits of ripretinib had already been taken into account.

Conclusion

Recommendation

3.19 The clinical-effectiveness evidence showed that ripretinib plus best supportive care improved key outcomes for people with advanced GIST who had had 3 or more kinase inhibitors, including imatinib. But the long-term survival estimates with ripretinib were very uncertain. The ICER that included the committees preferred assumptions was within the range that

NICE considers an acceptable use of NHS resources (see section 3.14). So, ripretinib can be used.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced gastrointestinal stromal tumours and the healthcare professional responsible for their care thinks that ripretinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Iolo Doull

Interim Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director or a principal technical adviser.

Zain Hussain and Victoria Gillis-Elliott

Technical leads

Alexandra Filby and Joanna Richardson

Technical advisers

Kate Moore

Project manager

Elizabeth Bell

Principal technical adviser

ISBN: [to be added at publication]