NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

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

1 Recommendations

1.1 Ripretinib is not recommended, within its marketing authorisation, for treating advanced gastrointestinal stromal tumour (GIST) in adults after 3 or more kinase inhibitors, including imatinib.

1.2 This recommendation is not intended to affect treatment with ripretinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for advanced GIST, after people have tried the kinase inhibitors imatinib, sunitinib and regorafenib, is best supportive care.

Clinical trial evidence shows that ripretinib increases the time before the cancer gets worse and increases how long people live compared with best supportive care.

Ripretinib meets NICE's criteria to be considered a life-extending treatment at the end of life. But the economic model does not reflect clinical practice about when to change treatment when advanced GIST gets worse, meaning it is not in line with how ripretinib would be used in the NHS. So it is not possible to work out if ripretinib is cost effective with the available analyses, so it is not recommended.

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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 (three 50 mg tablets). The company has a commercial arrangement, which would have applied if ripretinib had been recommended.

3 Committee discussion

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

The condition and treatment pathway

There is an unmet need for treatments for people with advanced GIST who have had 3 or more treatments

3.1 Gastrointestinal stromal tumour (GIST) is a rare cancer that affects survival and quality of life. The patient experts explained that advanced GIST causes debilitating symptoms including hand-foot syndrome, severe muscle cramps, diarrhoea and cardiac problems. GIST is treated using tyrosine kinase inhibitors, which are used sequentially and include:

- imatinib, then
- sunitinib if there is resistance or intolerance to imatinib, then
- regorafenib if the cancer progresses on the previous treatments or the previous treatments are intolerable.

In their submissions, the patient experts said that as the cancer progresses and the different treatments are tried, secondary mutations are more likely to develop. This can make treatment ineffective. The clinical experts added that there are no fourth-line treatment options for people if their cancer progressed or if they cannot tolerate the available options, other than best supportive care. The clinical experts noted that the only alternative to best supportive care was to take part in a clinical trial but these were rare. The patient and clinical experts also highlighted that there has been unmet need in this disease area for a long time, and that a new treatment option would be welcomed. The patient expert acknowledged the side effects of ripretinib but noted that they were more manageable than the side effects from some of the other tyrosine kinase inhibitors. The committee heard that, because of the limited treatment options for advanced GIST, clinicians aim to maximise the benefit of each treatment option before moving to the next treatment. The clinical experts also noted that it is not UK clinical practice to try treatments again. The committee concluded that there is an unmet need for an effective treatment option for advanced GIST if imatinib, sunitinib and regorafenib have already been tried.

Comparators

Best supportive care is an appropriate comparator for fourth-line ripretinib

3.2 The company included best supportive care as the only relevant comparator for ripretinib. But the ERG suggested that continued regorafenib after progression was also a relevant comparator. It pointed out that the National Comprehensive Cancer Network (NCCN) clinical

guidelines and the UK GIST guidelines support continuing tyrosine kinase inhibitors after disease progression when no further options are available. The clinical experts explained that determining disease progression is difficult and that both radiological and clinical progression are considered. Size and density of the tumours, treatment tolerability and clinical symptoms are all taken into account. The clinical experts said that because disease progression is difficult to define, people may continue having treatments after radiological progression. The experts also highlighted that there is evidence that continuing treatment with tyrosine kinase inhibitors after progression can slow further progression in some people. They noted that it's unlikely regorafenib would be widely used after disease progression. This is because, in their experience, it only has benefits for a limited time and is associated with toxicities that often outweigh any small increase in clinical benefit after progression. One clinical expert estimated that 1 in 3 people continue having regorafenib after radiological progression. The clinical lead for the Cancer Drugs Fund said that some people would have regorafenib if there is clinical benefit and because it is the last line of treatment. The committee recalled that, because of the limited treatment options, each treatment option is used until the maximum clinical benefit is gained before moving to the next treatment line (see section 3.1). But the clinical experts noted that, because ripretinib has a potential treatment benefit and less toxicity than regorafenib, it's possible people would be switched to it at an earlier point of disease progression, but only after gaining the maximum clinical benefit from regorafenib. The company and ERG agreed that there was limited data to inform an indirect treatment comparison of ripretinib and post-progression regorafenib. The committee acknowledged that, by not having a comparison with post-progression regorafenib, some uncertainty is added around how effective ripretinib is likely to be in the fourth-line treatment setting. But it concluded that best supportive care is likely the most appropriate comparator for this appraisal, given the available evidence.

Clinical evidence

Ripretinib plus best supportive care is more effective than placebo plus best supportive care

3.3 The clinical effectiveness evidence for ripretinib compared with best supportive care was from the INVICTUS trial. This was a phase 3, placebo-controlled, double-blind, randomised controlled trial that compared ripretinib plus best supportive care with placebo plus best supportive care. There were 129 adults in the intention-to-treat population, 10 were from the UK. In the trial, ripretinib was continued until disease progression or unacceptable toxicity. At disease progression, people could continue with their current ripretinib dose, double the dose, or stop. People having placebo plus best supportive care could leave the study or switch to ripretinib plus best supportive care at disease progression. Progression was defined by blinded independent central review, which the committee acknowledged was different to the nuanced decision making in clinical practice (see section 3.2). The trial's inclusion criteria involved at least 3 previous treatments and an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2. The trial stratified people according to the number of previous treatments and the ECOG performance score. The hazard ratio for overall survival was 0.41 (95% confidence interval [CI] 0.26 to 0.65) and the hazard ratio for progression-free survival was 0.16 (95% CI 0.10 to 0.27). This shows better overall survival and progression-free survival for people having ripretinib plus best supportive care than for people on placebo plus best supportive care. A clinical expert highlighted that the median progression-free survival of 6 months for ripretinib is notable, for a treatment given after 3 or more previous treatments. The committee concluded that ripretinib plus best supportive care is more effective than placebo plus best supportive care for people with advanced GIST after 3 or more treatments.

Data from the intention-to-treat population of the trial is appropriate for decision making

3.4 In its submission, the company used data from the intention-to-treat population from INVICTUS to model ripretinib as a fourth-line treatment (that is, after just 3 previous treatments). However, 37% of people in INVICTUS had 4 or more previous treatments. A clinical expert explained that, because INVICTUS was an international trial, off-label tyrosine kinase inhibitors could be used as later-line treatments. The ERG had concerns that the number of previous treatments could be a treatment effect modifier. But the company noted that the hazard ratios for progression-free survival for people who had 3 previous treatments were similar to those for people who had 4 or more previous treatments. The clinical experts said that few people in the NHS have access to more than 3 lines of treatment so people having treatment in the NHS are more likely to be fitter and have fewer resistant secondary mutations than those who had progressed to more than 4 lines of treatment in the clinical trial. So the cancer may respond better in people who have fewer than 4 previous treatments than in people who have 4 or more. The ERG also said that the number of previous treatments could be a prognostic factor. It noted that progression-free survival could be longer for people who have had fewer lines of treatment, or alternatively people who had 6 or 7 lines of treatment may have a better disease profile than those who have fewer. The ERG explained that, because there were only small numbers in the subgroups for number of previous treatments, it was difficult to conclude how this affected ripretinib's efficacy. The committee considered that the number of previous treatments was likely to be a treatment effect modifier or prognostic factor and so affect outcomes. How this might affect ripretinib's effectiveness in clinical practice was unclear. The committee recognised the limitations in the evidence but concluded that the data from the intention-to-treat population in the clinical trial was the best available and appropriate for decision making.

Cost effectiveness

A stopping rule is not appropriate

3.5 In its submission, the company presented a partitioned survival model with 3 health states to estimate the cost effectiveness of ripretinib plus best supportive care compared with placebo plus best supportive care. The 3 health states were progression-free, progressed disease and death. In the modelling, the company assumed that ripretinib was discontinued at disease progression with no further active treatment. Therefore the company assumed that time to treatment discontinuation was the same as progression-free survival. This assumption implies that in the model, treatment is stopped when there is radiological progression because progression-free survival from the trial was based on modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria. The committee was aware that ripretinib's summary of product characteristics says that treatment 'should continue as long as benefit is observed or until unacceptable toxicity'. It recalled that the clinical experts said that they continue using currently available tyrosine kinase inhibitors for GIST if there is clinical benefit and side effects are manageable, even if there is radiological progression (see section 3.2). The clinical lead for the Cancer Drugs Fund advised that implementing a stopping rule for ripretinib in the NHS would involve a modified RECIST based on progression and not clinical assessment. The company confirmed its position that progression would be based on radiological response rather than including clinical assessment. The clinical experts reiterated the nuanced decision-making process when determining progression in advanced GIST, which considers many factors (see section 3.2). They noted that in INVICTUS there was a 20% discrepancy rate in determining disease progression using blinded independent central review compared with clinical assessment, highlighting the difficulty in assessing disease progression. They added that it would be a difficult decision to stop treatment when there is still clinical benefit, despite radiological progression. The ERG

said that at the 2019 data cut in INVICTUS, 49% of people in the ripretinib arm continued open-label ripretinib and 31% of people in the ripretinib arm were still on double-blind ripretinib. So, the number of people continuing ripretinib after progression at the final data cut was between 49% and 80%. During the committee meeting the company noted that around 65% of people had continued ripretinib after progression but the committee was unclear if this was at the final data cut and whether the remaining people had stopped ripretinib or if their cancer had not progressed. The clinical lead for the Cancer Drugs Fund advised the committee that an expanded access programme for ripretinib was currently in place. The company confirmed that eligibility for this was in line with INVICTUS criteria, which allowed ripretinib to be used after radiological disease progression, in addition to double dosing. The clinical lead for the Cancer Drugs Fund highlighted the mismatch of the population in the expanded access programme with the company's intended population for ripretinib treatment using a stopping rule at disease progression. The committee noted that the company's stopping rule did not reflect clinical practice or current guidelines and was not clinically relevant. It also noted the consultation response from a patient organisation that said it did not support using radiological evidence alone to decide when to stop treatment. The company did not remove the stopping rule from its model in response to consultation. The committee concluded that the company's stopping rule does not align with the summary of product characteristics, or clinical practice, and disadvantages people with advanced GIST who may benefit from continued treatment after progression. Therefore, the stopping rule should not be included in the model.

The extrapolations of overall survival are highly uncertain

3.6 In its submission, the company adjusted overall survival to account for people in the best supportive care arm of INVICTUS switching to ripretinib after progression. But it did not adjust overall survival for people in the ripretinib arm continuing ripretinib after progression, at the standard dose or doubled dose. So the company assumed that overall survival was not

affected by ripretinib use after progression (see section 3.5). The ERG expected overall survival to be affected by ripretinib use after progression, because of clinical advice and the implausibility of the company's overall survival estimates for the ripretinib arm assuming best supportive care after progression on ripretinib. So the ERG preferred to use the company's scenario that adjusted overall survival for ripretinib use after disease progression using a simple 2-stage method with recensoring. The ERG's estimates of overall survival were more than 50% lower than the company's estimates of overall survival in the ripretinib arm, but the exact numbers are confidential so cannot be reported here. The clinical experts highlighted that it was difficult to predict the expected survival after progression with ripretinib. But they noted that if ripretinib follows the activity of other tyrosine kinase inhibitors in earlier lines of treatment for a kinase-driven cancer, then progression is expected to be similarly rapid after stopping treatment. The company acknowledged that the clinical experts' opinions were important to consider, and that it was plausible that there is a positive effect on overall survival from continuing to have ripretinib after disease progression. But it added that it did not find evidence from the INVICTUS data for a negative effect on overall survival if treatment was stopped at progression so did not include it in the modelling. The committee recalled that adjusting overall survival for ripretinib use after progression reduces the overall survival, as evidenced in the ERG's base case, but considered that even the adjusted overall survival estimates were optimistic. This is because the survival extrapolations did not have face validity (that is, the results were unexpected) when considering clinical expert opinion on overall survival estimates. The committee expressed concern about the extent to which the overall survival extrapolations reflected clinical practice. The ERG noted that further analyses adjusting overall survival for people in the ripretinib arm continuing ripretinib after disease progression could be explored, in addition to the simple 2-stage adjustment in the company's model, to give alternative results. The committee agreed that using

alternative approaches could help to reduce the uncertainty associated with adjusting the overall survival estimates to account for post-progression use of ripretinib when a stopping rule is used in the model. But the company did not provide any new evidence or analysis in response to consultation. The ERG was able to explore some alternative approaches to modelling treatment switching using the model the company provided at technical engagement. They said that this additional analysis still incorporated the stopping rule and so may not be suitable for decision making. The committee concluded that neither the company's nor the ERG's approaches to modelling overall survival were appropriate because the stopping rule should be removed, meaning the extrapolations for overall survival were not suitable for decision making (see section 3.5).

The economic modelling does not reflect expected clinical practice

3.7 The ERG explained that if a stopping rule was not applied in the model, it would expect data from the intention-to-treat population to be presented. This would only be adjusted for people switching to the ripretinib arm from the best supportive care arm, and use costs based on the extrapolated time to treatment discontinuation data. The committee noted that the dose escalation in INVICTUS meant that using data from the intention-to-treat population may mean overall survival is overestimated, and that it would not reflect ripretinib's licensed dose. A clinical expert added that doubling the ripretinib dose could improve progression-free survival but there is uncertainty about how that would affect overall survival because of uncertainty in the size of the population affected. The committee agreed that future extrapolations of overall survival modelling should be validated and reflect clinical practice. The committee considered that the current overall survival estimates for ripretinib after progression were uncertain and did not reflect clinical practice as described by the clinical experts. The committee said that it would have preferred to have seen analyses that aligned time to stopping treatment with the trial evidence because this would reflect ripretinib's anticipated use in clinical practice. The company did not provide any new evidence or analysis in response to consultation,

so the committee concluded that the economic modelling did not reflect expected clinical practice.

Health-related quality of life

The utility values are uncertain and scenario analyses for the company and ERG's preferred utility value should have been explored

3.8 In its model, the company preferred to use a post-progression utility value from INVICTUS, which excluded the health-related quality of life estimates for people who continued ripretinib after progression for both treatment arms. The ERG considered that this was not appropriate because this utility value was based on people who were randomised to best supportive care who did not switch to ripretinib after progression, which is a small number of people. The ERG also noted that the company's utility value for people in the progressed disease state was high and could lack face validity. Specifically, the ERG noted that if the utility value from INVICTUS was used for the post-progression state, then people progressing at fourth line have a higher utility than people progressing at earlier lines of the treatment pathway. Also, the reduction in the utility value for the post-progression state compared with the progression-free state was small. The ERG preferred to use a utility value of 0.647 from the GRID trial that was used in NICE's technology appraisal guidance on regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours. The company explained that it preferred to use estimates from INVICTUS because the GRID trial considers people having regorafenib, and ripretinib has better tolerability than regorafenib (see section 3.1). The clinical experts also noted that regorafenib is associated with considerable side effects, and the dose and schedule are often adjusted to manage side effects. They added that persistent hypertension, hand-foot syndrome, gastrointestinal side effects, diarrhoea, muscle wastage and fatigue are all side effects associated with regorafenib that can persist outside of regorafenib's short therapeutic window. In comparison, the clinical expert's view on the quality of life for

people progressing after ripretinib was more optimistic. Overall, the company considered that using the GRID trial utility value could introduce bias because the GRID trial was done in a different population and treatment setting. The committee noted the time period for the final EQ-5D assessment in INVICTUS, and that the utility value from INVICTUS may not capture the health-related quality of life for the post-progression state. The committee concluded that there were strengths and weaknesses associated with using either source of utility values and that it would like to see scenarios using both the company's and ERG's preferred utility value in the model. The company did not provide any new evidence or analysis after the first committee meeting. This meant no alternative scenarios using the utility values were explored. The committee concluded that the utility values used in the economic modelling were uncertain.

Costs in the model

It is appropriate to include drug wastage in the model

3.9 The ERG applied an average 0.25 of a pack wastage per person, translating to 7 days of wastage over a treatment course, in its preferred analysis. In its response to technical engagement, the company argued that wastage applies for less than 5% of people. The clinical lead for the Cancer Drugs Fund supported including drug wastage and considered that 0.25 of a pack wastage was modest. The clinical experts confirmed that drug wastage was likely to be low, and that 7 days of wastage was reasonable. The company did not incorporate drug wastage into its modelling after the first committee meeting. The committee concluded that it was appropriate to include drug wastage, and that the ERG's estimate of 0.25 wastage per person was plausible.

End of life

Ripretinib meets the end of life criteria

3.10 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal 2013. The company and ERG agreed that ripretinib does meet the end of life criteria based on:

- it being indicated for people with a short life expectancy (that is, less than 24 months)
- there being sufficient evidence that it can offer an extension to life (that is, a mean value of at least 3 months).

The committee concluded that ripretinib meets NICE's criteria to be considered a life-extending treatment at the end of life.

Cost-effectiveness estimate

No plausible cost-effectiveness estimates can be determined

3.11 NICE's guide to the methods of technology appraisal 2013 notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (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.

The committee agreed that there were issues with the company's modelling approach and validity of outputs. It noted the high level of uncertainty, specifically:

- that 37% of people in INVICTUS had 4 or more previous treatments, which is likely a treatment effect modifier or a prognostic factor of outcomes (see section 3.4)

- the model includes a stopping rule that does not reflect clinical practice (see section 3.5)
- the overall survival modelling extrapolations are not clinically valid (see section 3.6)
- the plausibility of the utility value for the ripretinib arm after progression (see section 3.8).

Ripretinib meets the end of life criteria (see section 3.10). However, after taking the above factors into account, the committee judged that the company's base-case ICER was not plausible and noted that adjusting overall survival for post-progression ripretinib use caused the ICER to exceed £100,000 per QALY gained. The exact ICERs the committee used for decision making included confidential discounts so cannot be reported here. Because all of the analyses contained a stopping rule that the committee found inappropriate, the committee did not consider any of the results further. To address the committee's preferred assumptions, several updates to the model were needed:

- removing the stopping rule because it is not clinically appropriate and disadvantages people with advanced GIST (see section 3.5)
- ensuring the outputs of the model are clinically validated and align with clinical opinion on survival estimates (see section 3.6)
- adjusting overall survival estimates to account for dose escalation and treatment switching in the INVICTUS trial (see section 3.7)
- including scenario analyses for both the company's and ERG's preferred utility values (see section 3.8)
- including the ERG's preferred drug wastage of 0.25 of a pack per person (see section 3.9).

The company did not provide any new evidence or analysis in response to consultation. So the committee was unable to consider any cost-effectiveness estimates that had been generated using its preferred assumptions. At the second committee meeting, the committee

reaffirmed that the available cost-effectiveness estimates remained implausible because of the issues described above.

Other factors

Equalities

3.12 No equalities issues were raised during the appraisal process. No potential equality issues were identified in the company submission. The committee concluded that there were no equalities issues relevant to the recommendation.

Ripretinib is not innovative beyond what is captured in the cost-effectiveness estimates

3.13 The company describe ripretinib as innovative because it:

- can broadly inhibit wild-type and KIT and PDGFRA mutations
- addresses an unmet need.

The committee acknowledged the company's position that ripretinib is innovative. However, it concluded, and the company agreed, that there were no additional benefits associated with ripretinib that had not been captured in the cost-effectiveness estimates.

Conclusion

Ripretinib is not recommended

3.14 The committee recalled that it did not have any cost-effectiveness estimates using its preferred modelling assumptions (see section 3.11). The available evidence did not indicate that ripretinib is an effective use of NHS resources, even when end of life weighting is applied. The economic model did not reflect clinical practice about when to stop treatment with ripretinib, and was not aligned with the NHS expanded access programme. So the committee concluded that it did not recommend ripretinib for treating advanced GIST after 3 or more treatments.

4 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

Chair

Stephen Smith
Vice Chair, technology appraisal committee D

NICE project team

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

Summaya Mohammad, Emily Leckenby
Technical lead

Elizabeth Bell, Caron Jones
Technical adviser

Kate Moore
Project manager

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