NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

© National Institute for Health and Care Excellence 2023. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Deciphera Pharmaceuticals**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. PAWS GIST

4. **Evidence Review Group critique of company comments on the ACD**

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

© National Institute for Health and Care Excellence 2023. All rights reserved. See Notice of Rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee - company	Deciphera Pharmaceuticals	Sections 3.6 and 3.7 state *"The extrapolations of overall survival are highly uncertain" and "The economic modelling should reflect expected clinical practice"* The company would like to reiterate that reimbursement for ripretinib is being sought up to progression only. UK clinicians at an advisory board held in August 2022 stated that when considering whether to continue treatment with ripretinib, clinicians would consider the patient's best interest, taking into account clinical benefit and tolerability. The clinicians advised that treatment would be stopped at clear progression. The company does not believe the level of evidence is sufficient to assume additional survival benefit when ripretinib is used post-progression. UK clinicians at an advisory board held in August 2022 were unable to predict the difference (if any) in survival in relation to INVICTUS data if treatment was stopped at progression. The log-normal curve was chosen to extrapolate OS based on having one of the lowest combined AICs and the best visual fit.	Thank you for your comment. The committee concluded it was not appropriate to implement a stopping rule at disease progression based on radiological response. Discussions around this, extrapolations of overall survival and the economic modelling can be seen in sections 3.5, 3.6 and 3.7 of the FAD.
2	Consultee - company	Deciphera Pharmaceuticals	Section 3.8 states that "*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*." However, as per Poole et al. 2015, the post-progression utility value from the GRID trial was independent of treatment and therefore was observed in some patients who were still receiving open-label regorafenib.[1] Therefore, side effects that led to the low value of 0.647 may not have been persisting outside of regorafenib's therapeutic window but may have in fact been as a result of regorafenib still being administered.	Thank you for your comment. Discussion around the side effects associated with regorafenib can be seen in sections 3.8 of the FAD.
3	Consultee - company	Deciphera Pharmaceuticals	Section 3.9 states that "*It is appropriate to include drug wastage in the model*" UK clinicians at an advisory board held in August 2022 stated patients would be closely monitored (every 28 days) in this heavily pre-treated setting. The prescription and supply would closely match the patients' level of progression so that wastage would be tightly controlled. Clinicians estimated that any wastage would affect fewer than 5% of patients.	Thank you for your comment. Discussion around drug wastage can be seen in section 3.9 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
4	Consultee - company	Deciphera Pharmaceuticals	Section 3.6 states that "*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*." Further methods to extrapolate are explored in the model. The cost-effectiveness model provided to the ERG has the option to adjust overall survival for people in the ripretinib arm continuing ripretinib after disease progression using the simple two-stage adjustment with re-censoring as well as the following methods: simple two-stage adjusted without re-censoring, complex two-stage adjusted with re-censoring, complex two-stage adjusted without re-censoring, rank preserving structural failure time model (RPSFTM) with re-censoring and RPSFTM without re-censoring.	Thank you for your comment. The ERG was appreciative of this feature being brought to its attention.
5	Consultee - company	Deciphera Pharmaceuticals	In the section "Why the committee made these recommendations', it is stated that: *"Clinical trial evidence shows that ripretinib increases the time before the cancer gets worse and how long people live compared with best supportive care."* It would be clearer if this was amended to "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".	Thank you for your comment. The FAD has been updated.
6	Consultee - company	Deciphera Pharmaceuticals	In Section 3.1, it is stated that: *"In their submissions, the patient experts said that, as the cancer progresses and the different treatments tried, secondary mutations are more likely to develop."* It would be clearer if that was amended to "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"	Thank you for your comment. The FAD has been updated.
7	Consultee - company	Deciphera Pharmaceuticals	In Section 3.1, it is stated that *"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. And it's not UK clinical practice to try treatments again."* It would be clearer if this was amended to ""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."	Thank you for your comment. The FAD has been updated.
8	Consultee – patient group	PAWS	**Relevant evidence:** The evidence in favour of Ripretinib as a fourth line treatment in GIST is robust and this is agreed by NICE. *"Ripretinib meets NICE's criteria to be considered a life-extending treatment at the end of life".*	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				recommendations.
9	Consultee – patient group	PAWS	**Interpretations of the evidence** The committee recommendation states the following: *"The economic model does not reflect clinical practice about when to stop treatment with ripretinib. This means it is not possible to work out if ripretinib is cost effective with the available analyses. So, it is not recommended".* The interpretation of the evidence would appear to be biased towards ripretinib being stopped purely upon the radiological evidence, rather than on the combination of **clinical and radiological evidence** which is the standard used internationally when identifying progression of disease in GIST cancer patients. It is this combination of parameters that seems to have been overlooked in this appraisal and instead the information that the experts delivered has been interpreted as follows: *"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.* With GIST it is possible to mistakenly interpret radiological changes as progression when it is in fact a response to treatment. Treating clinicians will continue to use a drug where there is benefit to a patient. When a treatment stops working it is standard practice to stop using the treatment. To clarify this point, the National GIST guidelines state: *"The **potential misinterpretation of the images produced by the complex tumour response patterns to TKIs can lead to a false diagnosis of progression**, which must be considered."* ***Response assessment is complex and early progression in particular should be confirmed by a team experienced in treating GIST.** Anti-tumour activity translates into tumour shrinkage in most patients, but some patients may show only changes in tumour "density" on imaging, these changes sometimes precede a reduction in tumour volume. Such changes in tumour radiological appearance should be considered as indicative of tumour response. **Tumour size may even increase in the short term but if tumour density on CT scan is decreased this may still indicate tumour response [48, 49].** Even the apparent 'appearance' of new lesions may be due to them becoming less dense, or cystic, especially in the liver. Therefore, both tumour size and tumour density on CT scan, or consistent changes on MRI or contrast-enhanced ultrasound, should be considered when determining tumour*	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			response. ^{18}F-FDG-PET has proved useful in the early assessment of tumour response, for example when prediction of the response is valuable, for example in the case of preoperative therapy, or when response is in doubt. However, a small proportion of GISTs have no FDG uptake. The absence of tumour progression at 6 months [50] is also equivalent to a tumour response. Conversely, tumour progression may not always be accompanied by changes in tumour size. For example, an increase in the tumour density shown by contrast enhancement within a previously responding low density tumour lesion, may be indicative of tumour progression. A typical progression pattern is the 'nodule within the mass', in which a portion of a responding lesion becomes hyper-dense [51]. *Isolated progression may be amenable to surgery or other local measures, such as radiofrequency ablation".* Treating GIST clinicians would stop using Ripretinib when it has clearly stopped working.	
10	Consultee – patient group	PAWS	Ripretinib is a valuable treatment option and as a fourth line treatment option substantially better than the alternative which sadly for GIST patients is best supportive care until death.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

	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):	Deciphera Pharmaceuticals
Disclosure 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]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

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	Sections 3.6 and 3.7 state *"The extrapolations of overall survival are highly uncertain" and "The economic modelling should reflect expected clinical practice"* The company would like to reiterate that reimbursement for ripretinib is being sought up to progression only. UK clinicians at an advisory board held in August 2022 stated that when considering whether to continue treatment with ripretinib, clinicians would consider the patient's best interest, taking into account clinical benefit and tolerability. The clinicians advised that treatment would be stopped at clear progression. The company does not believe the level of evidence is sufficient to assume additional survival benefit when ripretinib is used post-progression. UK clinicians at an advisory board held in August 2022 were unable to predict the difference (if any) in survival in relation to INVICTUS data if treatment was stopped at progression. The log-normal curve was chosen to extrapolate OS based on having one of the lowest combined AICs and the best visual fit.
2	Section 3.8 states that "*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*." However, as per Poole et al. 2015, the post-progression utility value from the GRID trial was independent of treatment and therefore was observed in some patients who were still receiving open-label regorafenib.[1] Therefore, side effects that led to the low value of 0.647 may not have been persisting outside of regorafenib's therapeutic window but may have in fact been as a result of regorafenib still being administered.
3	Section 3.9 states that "*It is appropriate to include drug wastage in the model*" UK clinicians at an advisory board held in August 2022 stated patients would be closely monitored (every 28 days) in this heavily pre-treated setting. The prescription and supply would closely match the patients' level of progression so that wastage would be tightly controlled. Clinicians estimated that any wastage would affect fewer than 5% of patients.
4	Section 3.6 states that "*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*." Further methods to extrapolate are explored in the model. The cost-effectiveness model provided to the ERG has the option to adjust overall survival for people in the ripretinib arm continuing ripretinib after disease progression using the simple two-stage adjustment with re-censoring as well as the following methods: simple two-stage adjusted without re-censoring, complex two-stage adjusted with re-censoring, complex two-stage adjusted without re-censoring, rank preserving structural failure time model (RPSFTM) with re-censoring and RPSFTM without re-censoring.
5	In the section "Why the committee made these recommendations', it is stated that: *"Clinical trial evidence shows that ripretinib increases the time before the cancer gets worse and how long people live compared with best supportive care."*

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

	It would be clearer if this was amended to "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".
6	In Section 3.1, it is stated that: *"In their submissions, the patient experts said that, as the cancer progresses and the different treatments tried, secondary mutations are more likely to develop."* It would be clearer if that was amended to "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"
7	In Section 3.1, it is stated that *"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. And it's not UK clinical practice to try treatments again."* It would be clearer if this was amended to ""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."

References

1. Poole CD, Connolly MP, Chang J, Currie CJ. Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. Gastric Cancer. 2015;18(3):627.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- 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 appraisal consultation document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

	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):	[redacted] PAWS-GIST
Disclosure 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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

	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	**Relevant evidence:** The evidence in favour of Ripretinib as a fourth line treatment in GIST is robust and this is agreed by NICE. *"Ripretinib meets NICE's criteria to be considered a life-extending treatment at the end of life".*
2	**Interpretations of the evidence** The committee recommendation states the following: *"The economic model does not reflect clinical practice about when to stop treatment with ripretinib. This means it is not possible to work out if ripretinib is cost effective with the available analyses. So, it is not recommended".* The interpretation of the evidence would appear to be biased towards ripretinib being stopped purely upon the radiological evidence, rather than on the combination of **clinical and radiological evidence** which is the standard used internationally when identifying progression of disease in GIST cancer patients. It is this combination of parameters that seems to have been overlooked in this appraisal and instead the information that the experts delivered has been interpreted as follows: *"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.* With GIST it is possible to mistakenly interpret radiological changes as progression when it is in fact a response to treatment. Treating clinicians will continue to use a drug where there is benefit to a patient. When a treatment stops working it is standard practice to stop using the treatment. To clarify this point, the National GIST guidelines state: *"The **potential misinterpretation of the images produced by the complex tumour response patterns to TKIs can lead to a false diagnosis of progression**, which must be considered."* ***Response assessment is complex and early progression in particular should be confirmed by a team experienced in treating GIST.** Anti-tumour activity translates into tumour shrinkage in most patients, but some patients may show only changes in tumour "density" on imaging, these changes sometimes precede a reduction in tumour volume. Such changes in tumour radiological appearance should be considered as indicative of tumour response. **Tumour size may even increase in the short term but if tumour density on CT scan is decreased this may still indicate tumour response [48, 49].** Even the apparent 'appearance' of new lesions may be due to them becoming less dense, or cystic, especially in the liver. Therefore, both tumour size and tumour density on CT scan, or consistent changes on MRI or contrast-enhanced ultrasound, should be considered when determining tumour response. ^{18}F-FDG-PET has proved useful in the early assessment of tumour response, for example when prediction of the response is valuable, for example in the case of preoperative therapy, or when response is in doubt. However, a small proportion of GISTs have no FDG uptake. The absence of tumour progression at 6 months [50] is also equivalent to a tumour*

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

	response. Conversely, tumour progression may not always be accompanied by changes in tumour size. For example, an increase in the tumour density shown by contrast enhancement within a previously responding low density tumour lesion, may be indicative of tumour progression. A typical progression pattern is the 'nodule within the mass', in which a portion of a responding lesion becomes hyper-dense [51]. *Isolated progression may be amenable to surgery or other local measures, such as radiofrequency ablation".* Treating GIST clinicians would stop using Ripretinib when it has clearly stopped working.
3	Ripretinib is a valuable treatment option and as a fourth line treatment option substantially better than the alternative which sadly for GIST patients is best supportive care until death.
4	
5	
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 links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- 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 appraisal consultation 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 21 December 2022. Please submit via NICE Docs.

Please return to: **NICE DOCS**

Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies.

Addendum: ERG comments on the company's ACD response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Katy Cooper, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	16th January 2023

1. Introduction

In November 2022, the National Institute for Health and Care Excellence (NICE) issued a negative Appraisal Consultation Document (ACD) for ripretinib for treating advanced gastrointestinal stromal tumour (GIST) in adults after 3 or more kinase inhibitors, including imatinib.[1] The NICE ACD states that the economic model does not reflect clinical practice about when to stop treatment with ripretinib and that this means it is not possible to work out if ripretinib is cost effective from the available analyses.

In December 2022, the company submitted a response to the NICE ACD.[2] The company's response includes a written document only. No additional economic analysis has been presented by the company. The company's ACD response document comments on the following issues:

1. Uncertainty around the modelled survival estimates for ripretinib and model functionality to assess alternative treatment switching adjustment methods (company's ACD response, points 1 and 4)
2. The utility value applied in the progressed disease (PD) health state (company's ACD response, point 2)
3. The inclusion of costs associated with drug wastage (company's ACD response, point 3).

The company's ACD response[2] (points 5-7) also provides some suggestions regarding minor alterations to the text contained in the NICE ACD.

This document provides a brief summary and critique of the three issues listed above. The Evidence Review Group (ERG) does not believe it is necessary to comment on the text amendments suggested by the company.

2. Summary and critique of key points discussed in the company's ACD response

2.1 1. Uncertainty around the modelled survival estimates for ripretinib and model functionality to assess alternative treatment switching adjustment methods

The company's ACD response[2] makes the following key points:

- The company reiterates that reimbursement is being sought for ripretinib only up to the point of disease progression.
- The company states that the clinicians they consulted advised that in clinical practice, treatment would be stopped at "clear progression" (the ERG notes that it is unclear whether this refers to radiological or symptomatic progression).
- The company does not believe that the level of evidence is sufficient to assume that ripretinib provides an additional overall survival (OS) benefit when used after disease progression.
- The company's model includes the functionality to assess alternative switching adjustment approaches in both treatment groups.

The ERG's concerns regarding the plausibility of the company's survival model predictions, as outlined in the ERG report[3] and the ERG's technical engagement (TE) response[4] remain unchanged – the ERG believes that the company's assumption that post-progression ripretinib use has not influenced OS is inappropriate and that the presence of uncertainty around the magnitude of this effect is not a reasonable justification for excluding adjustment altogether. The ERG's clinical advisors both believed that open-label ripretinib given after disease progression will have influenced OS in INVICTUS[5] and they did not consider the company's base case model (excluding OS adjustment in the ripretinib group) to provide plausible predictions of OS given the company's stopping rule whereby ripretinib is given only until disease progression. In addition, the ERG does not consider it plausible that patients with advanced GIST who have received at least 4 prior lines of therapy, who have progressed on ripretinib, and who then subsequently receive best supportive care (BSC) alone, will survive for an average of [redacted] years, as predicted by the company's original submitted model. The ERG's clinical advisors commented that if ripretinib was discontinued at progression, they would expect OS to be around 6 months longer than progression-free survival (PFS).

The ERG further notes that Section 3.5 of the NICE ACD[1] states that the Appraisal 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."* Given the Appraisal Committee's position on the stopping rule, the ERG believes that the most appropriate analysis would involve adjusting OS to account for the impact of treatment switching in the BSC group only, and estimating ripretinib treatment costs using parametric survival models fitted to the data on time to treatment discontinuation (TTD) in INVICTUS.[5] This analysis has not been presented by the company. As the TTD data INVICTUS have not been presented by the company at any point during this appraisal, the ERG is unable to undertake this analysis.

The company's ACD response[2] highlights that the submitted model includes the functionality to assess a range of alternative switching approaches in both treatment groups. At the technical engagement (TE) stage of the appraisal, the ERG had misunderstood that the drop-down menu for selecting the treatment switching adjustment approach in the executable model applies to both treatment groups if the "Adjust open label ripretinib arm" drop-down menu is also set equal to "yes". As such, the ERG has now been able to explore the impact of each of the alternative switching methods on the incremental cost-effectiveness ratio (ICER) for ripretinib versus BSC. The results of these additional scenario analyses are provided in Section 3. However, as the Appraisal Committee's preferred scenario involves removing the stopping rule, the ERG's additional analyses may not be relevant for decision-making.

2.2 Utility value applied in the progressed disease health state

The company's ACD response[2] states that the low utility value of 0.647 for the progressed disease (PD) state from the GRID trial (Poole *et al.*[6]) may be a result of the study design, as some patients were still receiving regorafenib at the point of disease progression.

The ERG agrees that the utility values reported by Poole *et al.*[6] are potentially subject to some level of confounding as open-label treatment with regorafenib was permitted in the placebo group after disease progression. As noted by the authors of the paper, *"Because there is substantial crossover of placebo subjects to active treatment, there is very limited opportunity to observe utility values for progressive disease in the presence of BSC."*

The company's ACD response[2] does not present any alternative health utility values for the PD state; as such, the ERG presumes that the company still prefers the utility value presented in the TE model of [redacted]. As outlined in the ERG's TE response,[4] the ERG has concerns regarding the use of this value because:

- It is based on a small sample size (N=[redacted]).
- It suggests that disease progression has only a minor impact on HRQoL (progression-free utility value = [redacted]; progressed disease utility value = [redacted]; disutility associated with progression = [redacted]). This may not be plausible.
- It may not reflect the patient's mean utility over their entire remaining survival time.

Section 3.8 of the NICE ACD[1] states that *"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 ERG's TE response presents analyses using both utility values for the PD state and indicates that the choice of utility value for the PD state does not substantially impact on the ICER (ERG preferred analysis using PD utility of 0.647, ICER = £134,241 per quality-adjusted life year [QALY] gained; ERG preferred analysis with higher PD utility of [redacted], ICER = £130,100 per QALY gained).

2.3 The inclusion of costs associated with drug wastage

With respect to costs associated with drug wastage, the company's ACD response[2] makes the same arguments as those presented in their TE response[7] – that wastage would be tightly controlled in practice and that clinicians consulted by the company estimated that any wastage would affect fewer than 5% of patients.

As noted in the ERG report[3] and the ERG TE response,[4] aside from any dose reductions or interruptions, some degree of wastage would be incurred by any patient taking an oral therapy if they stop treatment

for any reason (e.g., due to intolerance, progression, or death) before completing a pack of treatment. The ERG retains its view that some level of wastage should be included in the model. The ERG notes that Section 3.9 of the NICE ACD[1] states that *"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."*

3. Additional analyses undertaken by the ERG

Table 1 presents the results of additional exploratory analyses undertaken by the ERG using the company's updated model from the TE stage of the appraisal. With the exception of the company's preferred model at TE, each of these analyses includes OS adjustment for treatment switching in both treatment groups. The row heading for each analysis reports the modelled mean time spent alive with PD in the ripretinib group. Regardless of which method is used and whether re-censoring is included, the ICER remains higher than £50,000 per QALY gained across all analyses in which OS is adjusted in the ripretinib group. The ERG also notes that all of these alternative analyses suggest a mean PD survival duration for ripretinib which is considerably longer than the estimate provided by the ERG's clinical advisors (around 6 months). Because of this, the ERG does not consider any of these additional analyses to provide plausible predictions of OS for ripretinib, and the ERG's preferred analysis remains unchanged from that presented in the ERG report (ICER=£134,241 per QALY gained). In the absence of the TTD data from INVICTUS,[5] the ERG is unable to present an analysis which is consistent with the Appraisal Committee's preferences (i.e., no stopping rule).

Table 2: Impact of alternative switching methods applied to both treatment groups

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's TE model (BSC group adjusted using simple 2-stage method with re-censoring, ripretinib unadjusted), log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,280**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's TE model, both groups adjusted using simple 2-stage method without re-censoring, log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,518**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's TE model, both groups adjusted using simple 2-stage method with re-censoring, log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£89,362**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's TE model, both groups adjusted using complex 2-stage method without re-censoring, log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£56,787**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's TE model, both groups adjusted using complex 2-stage method with re-censoring, log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£63,873**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's TE model, both groups adjusted using RPSFT without re-censoring, log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£65,744**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's TE model, both groups adjusted using RPSFT with re-censoring, log-normal OS models. Modelled ripretinib PD survival time = [redacted] years.†							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£76,302**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG-preferred model EA5 (both groups adjusted using simple 2-stage method with re-censoring), generalised gamma OS models. Modelled ripretinib PD survival time = [redacted] years.							
Ripretinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£134,241**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

** Undiscounted*

†The company's TE model excludes drug wastage and applies a utility value for the PD state of [redacted]

4. References

1. National Institute for Health and Care Excellence. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments. Appraisal Consultation Document. NICE: London; 2022.
2. Deciphera Pharmaceuticals. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 or more treatments. Company's ACD response. Deciphera Pharmaceuticals: Bristol; 2022.
3. Tappenden P, Cooper C, Kearns B, Wong R, Rawdin A, Leaviss J. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies. A Single Technology Appraisal. University of Sheffield: Sheffield, UK; 2022.
4. Tappenden P, Cooper K. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies. Addendum: ERG comments on the company's technical engagement response. University of Sheffield: Sheffield; 2022.
5. Deciphera Pharmaceuticals. A Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have received treatment with prior anticancer therapies (INVICTUS). Clinical Study Report. Deciphera Pharmaceuticals: Waltham, MA; 2019.
6. Poole CD, Connolly MP, Chang J, Currie CJ. Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. *Gastric Cancer* 2015;18:627-34.
7. Deciphera Pharmaceuticals. Gastrointestinal stromal tumours (advanced) – ripretinib (after 3 therapies) [ID3805]. Company's technical engagement response. Deciphera Pharmaceuticals: Bristol, UK; 2022.