National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	GIST cancer UK	We think that the wording of the remit is rather confusing in the context of Ripretinib and its use according to the Marketing authorisation in GIST patients in the NHS in England (UK). In the NHS, GIST patients are offered **three lines of TKI therapy.** Imatinib, Sunitinib and then Regorafenib. GIST patients whose cancer progresses on these three lines of therapy or who cannot tolerate them, currently have no further treatment option unless they can access Ripretinib or other clinical trial drugs on compassionate use grounds. The scoping document aim should be: "To appraise the clinical and cost effectiveness of Ripretinib within its marketing authorisation **relevant to the NHS England treatment pathway** for advanced gastrointestinal stromal tumour (GIST) patients who have received previous treatment with tyrosine kinase inhibitors (TKI)".	Thank you for your comment. It is not standard wording for NICE scopes to refer to the NHS England treatment pathway in this way. The remit has been updated and now reads "To appraise the clinical and cost-effectiveness of ripretinib within its marketing authorisation for people with advanced gastrointestinal stromal tumours (GIST) who have had at least 3 prior therapies".

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	Deciphera	Please amend the remit to reflect the target population more accurately for ripretinib: Based on recent feedback from the EMA we would like to change the remit to "To appraise the clinical and cost- effectiveness of ripretinib within its marketing authorisation for people with advanced gastrointestinal stromal tumours (GIST) who have received at least 3 prior therapies."	Thank you for your comment. The remit has been updated and now reads "To appraise the clinical and cost-effectiveness of ripretinib within its marketing authorisation for people with advanced gastrointestinal stromal tumours (GIST) who have had at least 3 prior therapies".
Timing Issues	GIST Cancer UK	GIST patients whose disease has progressed beyond the current three lines of therapy, urgently need access to Ripretinib to treat their GIST cancer and prolong their lives.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.

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	Sarcoma UK	Ripretinib is an important new treatment beyond 3rd line for patients with GIST for whom no other options exist and therefore should be considered appropriately.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	Deciphera	There is a very high level of unmet need in the treatment of advanced GIST in people who have received at least 3 other therapies, given that there are currently no lines of pharmacological therapy recommended specifically for this population. As a cancer treatment, ripretinib should be considered within the timeframes set within the NICE TA process, to publish guidance on cancer drugs within 90 days of marketing authorisation.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
Additional comments on the draft remit	Deciphera	None	Thank you. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	GIST Cancer UK	We would amend sentence 2 of paragraph 1 to read as follows: "GIST's are aggressive tumours and unfortunately many patients develop advanced GIST disease where the cancer spreads to other parts of the body (such as the liver or peritoneum)."	Thank you for your comment. The wording of the background section is written as per the current NICE style to ensure consistency across all scopes and appraisals. No changes were made to this sentence.
	Sarcoma UK	The incidence data seems low. Information from PHE's Get Data Out for sarcoma showed that the average incidence of new cases was 800, compared to 650 in the background information.	Thank you for your comment. The background information has been updated to reflect the incidence of all GIST cases from this dataset.
	Deciphera	The background information is accurate.	Thank you. No action required.
The technology/ intervention	GIST Cancer UK	**In this section we suggest that the last sentence should read:** "It has been studied in the randomized "Invictus" trial as a 4th line treatment versus placebo for the treatment of adults who have advanced GIST which has progressed despite receiving **three prior therapies"**	Thank you for your comment. This error has been corrected in the scope.

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	Deciphera	The description of the technology is accurate.	Thank you. No action required.
Population	GIST Cancer UK	**No, the population has not been defined appropriately. We suggest that this section should read as follows:** **"Population(s):** Adults with advanced GIST who have received at least **three** TKI therapies or have documented intolerance to any of these treatments. (N.B. The Invictus trial included "gastrointestinal stromal tumours with progression on at least imatinib, sunitinib, and regorafenib).	Thank you for your comment. The NICE scope has been updated to reflect this population and now reads: "Adults with advanced GIST who have had at least 3 prior therapies or have documented intolerance to any of these treatments".
	Sarcoma UK	We believe that the population should be for patients with advanced GIST who have received at least three lines of TKI therapies, or documented intolerance. This is in direct reference to the published data from the INVICTUS trial exploring ripretinib versus placebo in patients with metastatic GIST following 3 or more lines of treatment (https://pubmed.ncbi.nlm.nih.gov/32511981/) This would fit with best practice in England where regorafenib is approved to be used third line. Currently there is no data directly comparing regorafenib with ripretinib.	Thank you for your comment. The NICE scope has been updated to reflect this population and now reads: "Adults with advanced GIST who have had at least 3 prior therapies or have documented intolerance to any of these treatments".

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	Deciphera	Please amend reflect the target population more accurately for ripretinib: “Adults with advanced GIST who have received at least 3 prior therapies”	Thank you for your comment. The NICE scope has been updated to reflect this population and now reads: “Adults with advanced GIST who have had at least 3 prior therapies or have documented intolerance to any of these treatments”.
	Bayer	The population of “adults with advanced GIST who have received at least two TKI therapies” seems to be in contradiction with the title and remit of this appraisal (i.e. “Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies”) and with the position at which ripretinib has been studied in the pivotal phase III trial INVICTUS, which included patients either previously progressed on imatinib, sunitinib, and regorafinib or that were intolerant to these drugs.	Thank you for your comment. The NICE scope has been updated to reflect this population and now reads: “Adults with advanced GIST who have had at least 3 prior therapies or have documented intolerance to any of these treatments”.
Comparators	GIST Cancer UK	Please remove all comparison of Ripretinib to Regorafenib.	Thank you for your comment. The

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		Regorafenib is the third line of treatment in the NHS. The only comparison that should be drawn for Ripretinib is as a 4th line treatment compared to "Best supportive care". This section should read as follows: Comparators: Established clinical management without Ripretinib including best supportive care.	comparators have been updated and now reads: "Established clinical management without ripretinib including best supportive care".
	Sarcoma UK	As outlined in the previous box, we believe that this should be considered after third line treatments or intolerance as per INVICTUS. As such, the only realistic comparator is established clinical management including best supportive care.	Thank you for your comment. The comparators have been updated and now reads: "Established clinical management without ripretinib including best supportive care".
	Deciphera	The only appropriate comparator is established clinical management without ripretinib including best supportive care.	Thank you for your comment. The comparators have been updated and now reads: "Established clinical management without ripretinib including best supportive care".
	Bayer	There needs to be clarity on the intended place of ripretinib in the GIST treatment pathway. Regorafenib is listed as a comparator in the draft scope. Regorafenib has been approved as a treatment option in third line for people with GIST whose disease has progressed on, or are not tolerant to, prior treatment with imatinib and sunitinib. However, the title of this appraisal is "Ripretinib for treating advanced gastrointestinal stromal tumours after 3	Thank you for your comment. The comparators have been updated and now reads:

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		therapies" and ripretinib has been indeed studied in a double-blind phase 3 trial (INVICTUS) against placebo which included patients either previously progressed on imatinib, sunitinib, and regorafenib or that were intolerant to these drugs. This points towards ripretinib being used in 4th line following treatment with regorafenib. In light of this, we suggest regorafenib is removed from the scope as a relevant comparator as the only relevant comparator in 4th line would be BSC in the current NICE approved treatment pathway.	"Established clinical management without ripretinib including best supportive care".
Outcomes	GIST Cancer UK	Yes	Thank you. No action required.
	Sarcoma UK	We agree with the main areas outlined, with emphasis on overall survival, progression free survival, and noting that ongoing stable disease is a meaningful indicator in patients with GIST. We would also expect a focus on tolerability of treatment and effects health-related quality of life as measured in INVITCUS.	Thank you. No action required.
	Deciphera	The outcomes are appropriate for capturing the most important health related benefits.	Thank you. No action required.
Economic analysis	GIST Cancer UK	Cannot comment	Thank you. No action required.
	Deciphera	Aspects of the economic analysis, such as the time horizon, will be detailed in the submission.	Thank you. No action required.
Equality and Diversity	GIST Cancer UK	We do not anticipate any person / people with certain characteristics to be excluded in the scoping document.	Thank you. No action required.
	Deciphera	There are no issues with the proposed remit and scope with regards to equality.	Thank you. No action required.

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Other considerations	GIST Cancer UK	None	Thank you. No action required.
	Deciphera	The description of other considerations is accurate.	Thank you. No action required.
Innovation	GIST Cancer UK	Yes, we consider Ripretinib to be innovative in the setting of relapsed/metastatic GIST and it has the potential to improve the survival and quality of life compared with no treatment or best supportive care.	Thank you for your comment. The appraisal committee will consider the extent to which ripretinib is innovative in its decision making. No action required.
	Deciphera	The introduction of ripretinib will be a step change in the management of advanced GIST. Ripretinib is a novel tyrosine kinase switch control inhibitor engineered to broadly inhibit KIT and PDGFRA mutated kinases by using a unique dual mechanism of action that regulates the kinase switch pocket and activation loop. Phase III trial results indicate ripretinib significantly improved median progression-free survival compared with placebo and had an acceptable safety profile in patients with advanced GIST who were resistant or intolerant to other approved treatments. At present, there are no pharmacological therapy recommended specifically for this population. Thus, in England and Wales, ripretinib could fulfil a high unmet medical need for kinase inhibitors that are effective against these mutant forms of KIT and PDGFRA.	Thank you for your comment. The appraisal committee will consider the extent to which ripretinib is innovative in its decision making. No action required.
Questions for consultation	GIST Cancer UK	The following references should be included in the references section: Lancet Oncol. 2020 Jul;21(7):923-934. J Clin Oncol. 2020 Oct 1;38(28):3294-3303.	Thank you for your comment. As per our current NICE style, the

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			references reflect the sources used when drafting the scope document. No changes were made.
	Sarcoma UK	Relevant comparators and outcomes – as above Best supportive care is multi-speciality input into end-of-life care. For adoption of this technology, it should only be considered via a sarcoma specialist centre, as outlined in the NHS England Service Specification for Sarcoma.	Thank you for your comment. The committee will consider the comparators, position and adoption of the technology in its decision making. No action required.
	Deciphera	Questions for consultation are covered in the above sections. A cost comparison is not relevant for this submission.	Thank you. No action required.
Additional comments on the draft scope	Deciphera	None	Thank you. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope.

British Society of Gastroenterology
Help Bladder and Bowel
Guts UK