National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Quizartinib for treating relapsed or refractory acute myeloid leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	Daiichi Sankyo	Slightly updated wording suggested: "To appraise the clinical and cost effectiveness of quizartinib within its intended marketing authorisation for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD-positive. "	Thank you for your comment. The wording of the draft remit is in line with previous scopes for acute myeloid leukaemia. No changes have been made.
Timing Issues	Daiichi Sankyo	Intended marketing authorization and launch of quizartinib as currently there are no approved treatment options available that are specifically targeted to treat relapsed and refractory FLT3-ITD AML patients.	Thank you, your comment has been noted. No changes have been made.
	Leukaemia Care	There are currently no other treatments approved for use within the NHS for relapsed or refractory AML. Survival is very poor for these patients and therefore, there is an urgent need for new treatments.	Thank you, your comment has been noted. No changes have been made.

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Additional comments on the draft remit	Daiichi Sankyo	Although the exact indication becomes clear later on in the remit, we suggest to also provide the same level of precision in the title, i.e. Single Technology Appraisal. Quizartinib for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD-positive. “	Thank you for your comment. The wording of the draft remit is in line with previous scopes for acute myeloid leukaemia. No changes have been made.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Daiichi Sankyo	The background information so far insufficiently focuses on the FLT3-ITD mutation and the particularly poor prognosis associated with it. Therefore, the text should not refer to the FLT3 mutation in general, but the FLT3-ITD mutation in particular. Moreover, more details on the nature of the poor prognosis of FLT3-ITD mutated relapsed or refractory AML patients should be provided. We suggest to therefore delete the following sentence: “The FLT3 mutation is associated with relatively poor prognosis because of disease relapse”. And replace with the following wording: “The FLT3-ITD mutation is among the worst single prognostic factors in AML, and is associated with high leukemic burden, more rapid relapse, increased relapse risk and rate, shorter duration of remission and decreased survival.”(1-17)	Thank you for your comments. The background section is intended to give a brief summary of the disease area and the wording is in line with other recent scopes for acute myeloid leukaemia. A brief explanation of the FLT3 mutation has been added.

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		In the sentence “Allogeneic stem cell transplant means that stem cells were donated by someone else, usually a sibling whose tissue type closely matches that patient’s.”, please state “immunological profile” instead of “tissue type”. (draft scope page 1 of 5 at the bottom) The NICE Draft Scope document mentions: “People with relapsed and refractory AML are offered chemotherapy regimens containing high-dose of cytarabine such as fludarabine, cytarabine, idarubicin, and filgrastim (FLAG-Ida). People who cannot tolerate or do not wish to receive high-dose cytarabine are offered intermediate dose cytarabine regimen (IDAC).” (draft scope page 2) Since high-dose cytarabine is mentioned as a component of FLAG-Ida, the second part of the sentence refers to alternative treatment combinations with intermediate dose cytarabine, of which mitoxantrone, etoposide, intermediate dose cytarabine (MEC) is one example. However, clinicians’ comments received refer to a broader range of therapies which may also contain low-dose cytarabine, amongst other forms of treatment. There is no indication of intermediate-dose cytarabine in single use in the United Kingdom, for which reason the description of Intermediate dose cytarabine (IDAC) within the NICE Draft Scope may be misleading. For this reason, please consider the following wording to replace the above paragraph: “In the past 40 years, little progress has been made in prolonging survival in patients with R/R AML.(18) Treatment options for this patient population are limited and salvage chemotherapy is largely ineffective.(19) Median survival with current treatment options, including high-dose cytarabine and mitoxantrone, etoposide, intermediate dose cytarabine (MEC), ranges from 3.3 to 6.1 months (13.2 – 24.4 weeks) in recent phase 3 clinical trial reports.”(18-21) In particular patients with R/R FLT3-ITD mutated AML	Thank you for your comment. The wording of this section has been amended.

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		represent a high unmet need population with a dismal prognosis as evidenced by low response rates, high risk of relapse and a shorter overall survival.(9, 17, 22-26) Based on conversations with clinicians, FLAG-Ida is reported to be by far the most commonly used treatment regimen in England and Wales. In addition, various treatment options exist for treatment of relapsed or refractory AML patients who have become resistant to FLAG-Ida as frontline induction treatment. Since no single preferred treatment option exists for these patients, the suggestion is to use the following wording: "People with relapsed or refractory AML are offered chemotherapy regimens containing high doses of cytarabine such as fludarabine, cytarabine, idarubicin, and filgrastim (FLAG-Ida). People who cannot tolerate or do not wish to receive high-dose cytarabine may be offered treatment combinations containing lower doses of cytarabine."	
	Leukaemia Care	The statement about 'the majority of new diagnoses were in people aged 85-89 and over' is incorrect – peak incidence is in people aged 85-89 but this does not mean the majority of people diagnosed are over this age. CRUK statistics demonstrate that two thirds of patients are 65+ years old at diagnosis. We would also like to clarify on the term 'type of leukaemia cells' used in the third paragraph. Is this referring to the AML subtypes/cytogenetic abnormalities found within the leukaemia cells?	Thank you for your comment. This section has been amended to clarify this refers to the 85-89 year old age group. The type of leukaemia refers to different AML subtypes.
The technology/ intervention	Daiichi Sankyo	Suggestion to add the following text: Quizartinib (Vanflyta, Daiichi Sankyo) is an oral, highly potent and selective FMS-like tyrosine kinase-3 (FLT3) inhibitor in development for the treatment	Thank you for your comment. The wording in this section is consistent with other

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		of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD positive (QuANTUM-R). It is also in development for the treatment of adults with newly diagnosed AML which is FLT3-ITD positive (QuANTUM-First). QuANTUM-R is a global, phase 3, open-label, multicenter, randomized, controlled trial evaluating the efficacy and safety of quizartinib vs salvage chemotherapy for the treatment of adults with relapsed or refractory AML which is FLT3-ITD positive. QuANTUM-First is a phase 3, randomized, double-blind, placebo-control global study to compare the effect of chemotherapy plus quizartinib versus chemotherapy plus placebo, and quizartinib as maintenance therapy versus placebo on event-free survival for the treatment of adults with newly diagnosed AML which is FLT3-ITD positive (QuANTUM-First). Quizartinib has not yet been approved for any indication in any country.	scopes for acute myeloid leukaemia. The scope does not normally include specific clinical trials. The clinical evidence for quizartinib will be explored in greater detail during the development of this appraisal. No changes have been made.
Population	Daiichi Sankyo	Adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD-positive.	Comment noted. No changes have been made.
Comparators	Daiichi Sankyo	The comparator so far states: Established clinical management without quizartinib including but not limited to cytarabine based chemotherapy • Fludarabine, cytarabine, idarubicin, and filgrastim (FLAG-Ida) • Intermediate dose cytarabine (IDAC) We recommend amending this as follows:	Thank you, your comment has been noted. The listed comparators has been amended.

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		"Established clinical management without quizartinib", i.e. without stating any specific regimens. No treatments are approved specifically for patients with R/R FLT3-ITD mutated AML and no specific recommendations exist in clinical guidelines.(27, 28) Rather, therapy as described in the guideline for R/R AML patients, needs to be tailored for each individual patient, taking into consideration their age, performance status, comorbidities, and cumulative toxicity from prior therapies.(28-31) Both National Comprehensive Cancer Network (NCCN) and European Leukemia Net (ELN) guidelines, include, among others, the following salvage chemotherapy treatments for patients with acute myeloid leukemia:(12, 28) • the combination of granulocyte colony stimulating factor (G-CSF), fludarabine, cytarabine and idarubicin (FLAG-Ida), • the combination of mitoxantrone, etoposide and intermediate-dose cytarabine (MEC) or • Low-dose cytarabine (LDAC). An NHS England Evidence Review for clofarabine in R/R AML (in consultation) also considered a wide range of treatment options including those above in its treatment recommendations.(30) In the QuANTUM-R trial the investigator pre-selected a salvage chemotherapy regimen for each subject before randomization. At the UK sites of this trial, this included FLAG-Ida, MEC and LoDAC, i.e. all three salvage chemotherapy options provided.(32) The selection of low-dose cytarabine as a treatment option amongst UK clinicians, points to the fact that therapeutic options in relapsed or refractory (R/R) AML and specifically R/R FLT3-ITD-positive AML should not be limited	

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		to treatment combinations with high-dose or intermediate-dose cytarabine alone. This finding is also supported by clinician feedback. The selection of a broad array of regimens and treatment combinations as salvage chemotherapy at UK QuANTUM-R sites supports the notion that various alternative treatment options exist, and that alternative therapeutic choices are made by the treating clinician, depending on a patient's age, performance status, type and time to relapse on prior therapy, a patient's treatment history as well as prior receipt of an allogeneic stem cell transplant. Due to lack of response to salvage chemotherapy commonly recommended for AML, the comparator should cover the diversity of available therapies, i.e. both aggressive and milder treatments. Hence, we suggest amending the comparators to "Established clinical management without quizartinib" without listing each available regimen individually.	
	Leukaemia Care	Patients will often be put onto clinical trials in the relapsed or refractory setting as there are limited other options.	Thank you, your comment has been noted. No changes have been made.
Outcomes	Daiichi Sankyo	The current text in the NICE draft scope states: The outcome measures to be considered include: • overall survival • progression free survival • time to disease progression • response rates, including haematologic response	Thank you for your comment. The outcomes listed are examples and not intended to be an exhaustive list. The list has been amended in line with the main outcomes reported in

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		• blood-transfusion independence • stem cell transplant • infections • adverse effects of treatment • health-related quality of life Please change this as follows: The outcome measures to be considered include: • overall survival • event-free survival • response rates, including - composite complete remission (CRc) rate - duration of CRc - overall response rate (ORR) • Number of blood transfusions • stem cell transplant rate • infections • adverse effects of treatment • health-related quality of life Specifically, the requested changes consist of the following:	the trial. Complete remission and its duration is captured as part of response rates.

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		Please include Event-Free survival (EFS) as this was the pre-defined secondary endpoint. EFS was defined as “time from randomization until documented refractory disease, relapse after CRc, or death from any cause, whichever is observed first.” Please delete progression-free survival (PFS) and time to disease progression, since EFS is the relevant outcome measure in the AML indication. Please provide more precision around the response rates as outlined above, adding composite complete remission (CRc) as an outcome.	
Economic analysis	Daiichi Sankyo	No comments	Noted.
Equality and Diversity	Daiichi Sankyo	Daiichi Sankyo are not aware of any issues of inequality in the management of AML in England and Wales.	Thank you, this has been noted.
Other considerations	Daiichi Sankyo	No comments	Noted.
Innovation	Daiichi Sankyo	Current treatment options in R/R FLT3-ITD mutated AML are limited and have proven to be largely ineffective in these heavily pre-treated relapsed or refractory patients.(17, 23) Midostaurin, which has recently been recommended by the NHS as frontline treatment in FLT3-mutated AML patients, had previously failed to gain approval in the relapsed or refractory AML setting.(33, 34) This points to the selectivity and potency of quizartinib as a second-generation FLT3-inhibitor. (35)	Thank you, this has been noted. No changes have been made.

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		Quizartinib as single oral therapy represents a new targeted treatment for FLT3-ITD-positive patients. Results from the QuANTUM-R study are the first Phase 3 results to demonstrate significantly prolonged overall survival of a targeted FLT3-inhibitor vs. salvage chemotherapy in this specific patient population.(35) With these data, quizartinib has demonstrated the potential to impact a significant and meaningful change in overall survival for relapsed or refractory FLT3-ITD mutated AML patients and therefore represents a step change in the management of these patients.	
Questions for consultation	Daiichi Sankyo	• Have all relevant comparators for quizartinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for treating relapsed or refractory acute myeloid leukaemia? As stated above, no specific treatment recommendations exist in clinical guidelines for patients with R/R FLT3-ITD mutated AML. Treatment is individualised to the patient and includes a range of options. We suggest amending the comparators to “Established clinical management without quizartinib” without listing each available regimen individually. • Are the outcomes listed appropriate? See section “Outcomes” above, regarding suggested inclusions of the endpoint event-free survival (EFS), more precision around response rates with the inclusion of composite complete remission (CRc) and removal of progression-free survival (PFS) and time to progression. • Are there any subgroups of people in whom quizartinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?	Thank you for your comments, these have been noted. Changes have been made to the background and outcomes sections as described above.

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		The benefits associated with quizartinib are observed for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD-positive. • Where do you consider quizartinib will fit into the existing Blood and bone marrow cancers (2018) NICE pathway? Quizartinib should be considered in line with its anticipated indication for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD-positive. • Do you consider quizartinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes - See section "Innovation" above. • Do you consider that the use of quizartinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No. • Would it be appropriate to use the cost comparison methodology for this topic? No, overall survival is the key driver of clinical and economic benefit of quizartinib. • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? The QuANTUM-R study is the first Phase 3 trial to demonstrate significantly prolonged overall survival of a targeted FLT3-inhibitor vs. salvage	

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		chemotherapy. In addition, superior clinical efficacy has been proven in terms of higher CRc rates, higher ORR rates and higher stem cell transplantation rates (35). • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? The primary outcome for the trial was to determine whether overall survival (OS) is prolonged with quizartinib compared to salvage chemotherapy, for the treatment of adults with relapsed or refractory acute myeloid leukemia (AML) which is FLT3-ITD-positive. The primary outcome used in the trial, OS, is considered clinically relevant for this population, and is the key driver of clinical benefit in the economic model. • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? QuANTUM-First is a phase 3, randomized, double-blind, placebo-control global study. The purpose of this study is to compare the effect of quizartinib versus placebo (administered with standard induction and consolidation chemotherapy, then administered as maintenance therapy for up to 12 cycles) on event-free survival in subjects with FLT3-internal tandem duplication (ITD) positive AML.(36) The QuANTUM-FIRST trial therefore focusses on the frontline AML setting for treatment of FLT3-ITD-positive patients fit for intensive chemotherapy	
Additional comments on the draft scope	Daiichi Sankyo	Should further discussion on the comparators or treatment pathway be desired/needed, we would suggest to organise a scoping workshop on the topic with clinical experts.	Noted.

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

Department of Health and Social Care, Lymphoma Action and Pfizer