

# Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta1013](https://www.nice.org.uk/guidance/ta1013)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Recommendations

1.1 Quizartinib is recommended, within its marketing authorisation, as an option for newly diagnosed FLT3-ITD-positive acute myeloid leukaemia (AML) in adults, when used:

- with standard cytarabine and anthracycline chemotherapy as induction treatment, then
- with standard cytarabine chemotherapy as consolidation treatment, then
- alone as maintenance treatment.

Quizartinib is only recommended if the company provides it according to the [commercial arrangement](#).

## Why the committee made this recommendation

Usual treatment for newly diagnosed FLT3-ITD-positive AML is midostaurin with chemotherapy as induction and consolidation treatment, then alone as maintenance treatment. After consolidation treatment, people may have a stem cell transplant.

Evidence from a clinical trial shows that quizartinib plus standard chemotherapy increases how long people live compared with placebo plus standard chemotherapy. Quizartinib has not been directly compared in a clinical trial with midostaurin. Results from indirect comparisons mostly suggest there is no difference in how long people having quizartinib live, or how likely it is that their AML will come back, compared with midostaurin. But these results are uncertain because:

- the people in the midostaurin trial were younger than the people who would have quizartinib in the NHS, and clinical practice has changed since the trial was done
- some important characteristics between people in the trials could not be compared.

Because of the uncertainties in the clinical evidence, the cost-effectiveness estimates are uncertain. But the most likely estimates are within the range that NICE considers an acceptable use of NHS resources. So, quizartinib is recommended.

## 2 Information about quizartinib

### Marketing authorisation indication

- 2.1 Quizartinib (Vanflyta, Daiichi Sankyo) is indicated 'in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by Vanflyta single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive'.

### Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics for quizartinib](#).

### Price

- 2.3 The list prices of quizartinib are £6,451 for a 28-pack of 17.7 mg tablets, and £12,902 for a 56-pack of 26.5 mg tablets (excluding VAT; BNF online accessed August 2024).
- 2.4 The company has a [commercial arrangement](#). This makes quizartinib available to the NHS with a discount. The size of the discount is commercial in confidence.

## 3 Committee discussion

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

### The condition

#### New treatment option

- 3.1 The patient experts explained that there is an unmet need for new treatments for acute myeloid leukaemia (AML). They said that current treatment is very gruelling and so people who have AML want to know that the treatment will be beneficial. They explained that even a small increase in survival would be important to people with AML. Around 27% of people with AML have the FLT3-ITD mutation. Quizartinib is a targeted treatment for the FLT3-ITD mutation. It is indicated for induction, consolidation and maintenance treatment, and could also be used in the maintenance phase after a stem cell transplant, unlike current targeted treatments. The committee concluded that people with FLT3-ITD-positive AML would welcome a new treatment option.

### Clinical management

#### Comparators

- 3.2 For people who can have intensive chemotherapy, initial treatment for FLT3-ITD-positive AML is normally midostaurin with standard chemotherapy for induction and consolidation. Some people then have a stem cell transplant. After stem cell transplant, people may have sorafenib maintenance treatment, which is recommended through an [NHS England clinical commissioning policy](#). Midostaurin cannot be used for maintenance treatment after a stem cell transplant. For people who have not had a stem cell transplant, midostaurin can be used alone as maintenance treatment after a complete response. The clinical

experts said that they would not offer standard chemotherapy alone for anyone with FLT3-ITD-positive AML and that people would likely either have midostaurin or take part in a clinical trial. The committee concluded that midostaurin with standard chemotherapy was the most relevant comparator.

## Clinical effectiveness

### Clinical trial

- 3.3 The clinical evidence for quizartinib came from QuANTUM-First, a phase 3, randomised controlled trial that compared quizartinib plus standard chemotherapy with placebo plus standard chemotherapy. The primary outcome was overall survival, and in the study, overall survival was statistically significantly better with quizartinib than with placebo (hazard ratio 0.78; 95% confidence intervals [CI] 0.62 to 0.98). The committee concluded that quizartinib improved overall survival compared with placebo.

### Indirect treatment comparisons

- 3.4 Because there was no study that directly compared quizartinib with midostaurin, the company did an indirect comparison. It used a matched-adjusted indirect comparison (MAIC) to compare the results for quizartinib from QuANTUM-First with results for midostaurin from the RATIFY trial. The RATIFY trial compared midostaurin plus chemotherapy with placebo plus chemotherapy in people with FLT3-positive AML, using the placebo arm as an anchor. The company presented MAIC results for 3 outcomes:

- overall survival: hazard ratio 0.82 (95% CI 0.48 to 1.39)
- complete remission: odds ratio 0.92 (95% CI 0.42 to 1.97)
- cumulative incidence of relapse: hazard ratio 0.42 (95% CI 0.20 to 0.91).

The EAG highlighted that 1 of the limitations of a MAIC is that the results are applicable to the comparator population. In this case, they considered that

highly inappropriate, because RATIFY only included people aged under 60, which did not reflect the population in the NHS who may be eligible for quizartinib. Also, RATIFY was done between 2008 and 2016. The clinical experts agreed with the EAG that changes in clinical practice since then, meant the results of RATIFY were not likely to be generalisable to current NHS practice.

The company also did a multilevel network meta-regression (ML-NMR), the results of which can be applicable to any specified target population. It presented ML-NMR results for the same 3 outcomes:

- overall survival: hazard ratio 1.02 (95% CI 0.67 to 1.56)
- complete remission: odds ratio 0.63 (95% CI 0.34 to 1.19)
- cumulative incidence of relapse: hazard ratio 0.49 (95% CI 0.23 to 1.00).

The EAG considered that the results of the ML-NMR could be applicable to the NHS population. But it still had some concerns with both the MAIC and the ML-NMR. For example, several key characteristics could not be compared between the 2 trials because of differences in reporting. RATIFY only reported complete-remission results, but composite complete remission is more relevant to NHS practice. Also, cumulative incidence of relapse was analysed within a subset of people whose AML had reached complete remission, which meant the randomisation of the trials was broken. The EAG did a naive ML-NMR comparison, which suggested that the population adjustments applied within the company's ML-NMR favoured quizartinib over midostaurin, particularly in the cumulative-incidence-of-relapse analysis. The committee noted that most of the results from both indirect treatment comparisons did not show a statistically significant improvement with quizartinib over midostaurin, except for the MAIC result for cumulative incidence of relapse. One of the clinical experts said that it was often difficult to interpret overall survival outcomes because there were many factors to consider. They said that the rate of relapse was the most important outcome. They added that it was plausible that the rate of relapse could be lower with quizartinib compared with midostaurin, considering it was targeted specifically for the FLT3-ITD mutation. The committee concluded that the results of both indirect treatment comparisons were highly uncertain. But it

agreed that the results of the ML-NMR were more applicable to the population in the NHS who would be eligible for quizartinib.

## Maintenance after stem cell transplant

### Sorafenib as maintenance treatment

3.5 Sorafenib is recommended for maintenance treatment after stem cell transplant, through an NHS England clinical commissioning policy. The company did not include sorafenib as a comparator in the maintenance phase of treatment in its original submission. But after the clarification stage of this evaluation, it provided an unanchored MAIC to compare overall survival outcomes for quizartinib and sorafenib as maintenance treatment after a stem cell transplant. The MAIC used data from QuANTUM-First and the SORMAIN trial, which was a randomised controlled phase 2 trial comparing sorafenib with placebo in people with FLT3-ITD-positive AML. The company considers the results of the MAIC to be confidential so they cannot be reported here. The EAG cautioned that, because QuANTUM-First was not designed to estimate the efficacy and safety of quizartinib in the separate phases of treatment, the efficacy of quizartinib as maintenance treatment was uncertain. But the EAG considered that there was a lack of evidence for using sorafenib after midostaurin and that there were also several other uncertainties in the methods used in the MAIC. The clinical experts explained that there were difficulties with using sorafenib in this population because of the toxicity of sorafenib and the complications associated with transplant. They agreed that treatment with sorafenib varied across the NHS but that a substantial number of people had treatment with it. The committee concluded that sorafenib was a relevant comparator but that it was difficult to compare quizartinib with sorafenib in the maintenance phase of treatment.

## Economic model

### Company's modelling approach

3.6 The company presented a state-transition model, which included first- and second-line treatment. In first-line treatment, there were health states for induction, refractory, complete remission, relapse, stem cell transplant, post-stem cell transplant relapse and death. The model also included a cure point at around 3 years for people still in the complete-remission or stem-cell-transplant health states. A standard mortality ratio of 2 was applied to the general population mortality after this. The baseline characteristics in the company's model were based on the QuANTUM-First population but adjusted to effectively represent the RATIFY population. The company's model included standard chemotherapy, midostaurin and quizartinib arms. The EAG noted that overall survival from the QuANTUM-First trial was not directly used in the model. Instead, overall survival was determined by the rates of remission, relapse, refractory disease and stem cell transplant that were used to inform the transition probabilities between health states. In the company's base-case model, many of the transition probabilities between health states were informed by results from the MAIC. The EAG highlighted that the company's base-case model predicted substantial gains in life years and quality-adjusted life years (QALYs) for quizartinib compared with midostaurin. This was largely driven by the result of the MAIC for cumulative incidence of relapse (hazard ratio 0.42, see [section 3.4](#)). The EAG also had further concerns about the way the results of the indirect treatment comparisons had been applied in the economic model, including assuming proportional hazards when the data indicated that the proportional hazards assumption was violated. The committee was concerned that the QALY gains in the model were driven by the MAIC for cumulative incidence of relapse, which it had agreed was very uncertain (see [section 3.4](#)). It agreed that the results from the company's base-case model did not appear to reflect the results of the indirect treatment comparisons of overall survival. The committee concluded that the results from the company's base-case model were highly unreliable and lacked face validity.

## Modelling of second-line treatment

- 3.7 In the company's model, people with relapsed or refractory AML had second-line treatment with gilteritinib or FLAG-Ida (fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin). This was dependent on whether they had previously had midostaurin, quizartinib or standard chemotherapy alone as first-line treatment. In second-line treatment, there were health states for complete remission, relapse, stem cell transplant, and post-stem cell transplant maintenance. Transition probabilities between states were informed by the ADMIRAL trial, which compared gilteritinib with chemotherapy in relapsed or refractory FLT3-positive AML. The company did not model a cure in the second-line treatment setting, although a cure model had been accepted in [NICE's technology appraisal guidance on gilteritinib for treating relapsed or refractory AML](#). The EAG commented that a state-transition model was difficult to populate without individual patient-level data, and it preferred to use a nested partitioned survival model for second-line treatment. The EAG's model included the possibility of cure with second-line treatment and it assumed that 90% of people would have gilteritinib, based on clinical advice that most people would have gilteritinib in NHS practice. The NHS England Cancer Drugs Fund lead agreed that most people with relapsed or refractory FLT3-positive AML would have gilteritinib. The committee concluded that the EAG's modelling of second-line treatment was more appropriate than the company's because it better reflected both the previous evaluation of gilteritinib and expected NHS clinical practice.

## Time on treatment

- 3.8 In the company's base-case model, time on treatment was calculated using a restricted mean. It modelled a single-mean relative dose intensity across all treatment phases. But, in QuANTUM-First relative dose intensity differed across the treatment phases. The EAG considered that time on treatment, and so also medicine costs, were underestimated in the company's base case. The company provided a scenario analysis to address the EAG's concerns, but it did not include this in its base case. The EAG made some corrections to the company's scenario analysis and included this in its base-case model. The EAG also noted that although quizartinib is indicated for up to 36 cycles of treatment in the maintenance phase, in QuANTUM-First, most people did not have the full

36 cycles. The EAG highlighted that if people took quizartinib for more cycles in clinical practice than in the trial, this would increase the costs of quizartinib compared with the modelled costs. The committee concluded that the EAG's updated time-on-treatment analysis should be included in the model. But it noted that there was still uncertainty about the relative dose intensity of quizartinib that would be seen in clinical practice. This was because of the uncertainty around potential length of treatment in the maintenance phase in clinical practice.

## Changes to the model in the EAG base case

3.9 The EAG explained that it had also made the following changes to the company's model in its preferred base case:

- Instead of using the RATIFY-like population (see [section 3.6](#)) and transition probabilities informed by the MAIC results, the EAG base-case model was based on the QuANTUM-First population. This increased the mean age of people at the start of the model from 47 to 54. The relapse and overall survival data was based on the ML-NMR results. To model transitions from the first-line complete-remission health state, the company extrapolated outcomes for quizartinib in the RATIFY-like population, and applied hazard ratios from the MAIC to the quizartinib curve for the standard chemotherapy and midostaurin arms. The EAG used unadjusted QuANTUM-First data to model transitions for the standard chemotherapy and quizartinib arms. For the transition to relapse with midostaurin, the EAG applied the hazard ratio from the ML-NMR to the standard chemotherapy arm. For overall survival the EAG assumed mortality rates were the same for midostaurin and quizartinib after complete remission.
- The EAG reconfigured the induction health state, which avoided some of the problems in the company's model that were caused by using complete remission as a proxy for composite complete remission (because composite complete remission was not reported in RATIFY).
- The EAG used Kaplan–Meier data to model relapse after first-line stem cell transplant. The company had used a time-varying approach for overall survival after stem cell transplant, but time-invariant transition probabilities for relapse after stem cell transplant. The EAG considered this to be

inconsistent.

- The company's base case included utility values informed by several sources from the literature. The EAG preferred to use EQ-5D data from QuANTUM-First.

The EAG's base-case model predicted some incremental gains in QALYs with quizartinib compared with midostaurin, but these were smaller than in the company's model. The EAG explained that this was driven partly by the results of the ML-NMR for cumulative incidence of relapse, and partly by the assumed benefit of quizartinib in the maintenance treatment phase. The committee agreed that the EAG's model was more appropriate for decision-making because:

- it better reflected the population expected to be eligible for quizartinib in NHS practice
- it took a consistent approach to modelling overall survival and relapse after stem cell transplant
- it was in line with the reference case for NICE health technology evaluations.

But the committee was still concerned that it had not seen robust evidence to support the predictions, made by both the company's and EAG's base-case models, that:

- the relapse rate would be lower with quizartinib than with midostaurin
- quizartinib would increase QALYs compared with midostaurin.

## Relative rates of relapse

3.10 The committee considered a scenario analysis that set the rate of relapse for midostaurin to be equivalent to that of quizartinib. In the results of this scenario analysis, there was a small increase in QALYs with quizartinib compared with midostaurin. The committee acknowledged that this scenario was based on limited clinical evidence. But it agreed that there was uncertainty in the indirect treatment comparisons, and wide confidence intervals around most of the

results. So, it was plausible that the rates of relapse with quizartinib and midostaurin could be equivalent.

## Cost-effectiveness estimates

### Acceptable ICER

3.11 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- The indirect treatment comparisons were very uncertain because of key differences between the trials compared, including the age range included in RATIFY and the time period in which it was done (see section 3.4).
- Most of the results of the indirect comparisons did not show any statistically significant benefits with quizartinib compared with midostaurin (see section 3.4).
- The company's economic model did not include overall survival directly from the QuANTUM-First trial or from the indirect treatment comparison results, but assumed that rate of relapse was a surrogate for overall survival (see section 3.6).
- The company's base-case results showed substantial increases in overall survival with quizartinib compared with midostaurin, which was largely driven by the highly uncertain results of the MAIC for relapse. This did not reflect the results of the MAIC for overall survival (see section 3.6).

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

## Company and EAG cost-effectiveness estimates

3.12 The cost-effectiveness results are confidential because they include confidential discounts for quizartinib, the comparators and the subsequent treatments. The company's probabilistic base-case ICER for quizartinib compared with midostaurin was below £20,000 per QALY gained. The committee considered that the incremental QALYs predicted by the company's base-case model were too high, based on the evidence it had seen. The EAG made several changes to the model, which were:

- using a partitioned survival model for second-line treatment and assuming 90% of people had gilteritinib as second-line treatment (see [section 3.7](#))
- including the updated analysis of time on treatment (see [section 3.8](#))
- basing the model on the QuANTUM-First population, including changing the mean age, reconfiguring the induction state, and basing transitions between health states on QuANTUM-First data and the ML-NMR results (see [section 3.9](#))
- using Kaplan–Meier data for relapse after stem cell transplant (see [section 3.9](#))
- basing utility values on the EQ-5D data from QuANTUM-First (see [section 3.9](#)).

The EAG's deterministic base-case ICER for quizartinib compared with midostaurin was below £20,000 per QALY gained. The scenario analysis that assumed an equivalent rate of relapse for midostaurin and quizartinib (see [section 3.10](#)) resulted in a deterministic ICER that was also below £20,000 per QALY gained. The committee agreed it would have preferred to have seen probabilistic ICERs because of the uncertainty. But it noted that the EAG had been unable to produce probabilistic ICERs in its revised model structure without access to individual patient-level data. The committee agreed that it was uncertain whether quizartinib improved the rate of relapse, because of the lack of statistical significance in the indirect treatment comparison results. But it also agreed that the point estimates were improved with quizartinib and so a small incremental QALY could be plausible. The committee concluded that the most plausible ICER range was bounded by

the EAG's base case and the EAG's scenario analysis that assumed an equivalent rate of relapse for midostaurin and quizartinib.

## Other factors

### Severity

3.13 NICE's methods on conditions with a high degree of severity did not apply.

### Equality

3.14 One stakeholder highlighted that midostaurin appeared to be associated with a survival improvement in men but not women (in a subgroup analysis of RATIFY), but quizartinib may favour survival in women (in a subgroup analysis of QuANTUM-First). But the stakeholder considered that there was not currently enough evidence for this to be a consideration. Another stakeholder noted that although QuANTUM-First included people aged 18 to 75, quizartinib should be evaluated for all adults. Age and sex are protected characteristics under the Equality Act 2010. The committee noted that it would evaluate quizartinib within its marketing authorisation indication, which is for adults and does not have an upper age limit. Because the recommendation is for quizartinib in line with its marketing authorisation, the committee considered that its recommendation did not have a different effect on people protected by the equality legislation than on the wider population.

### Uncaptured benefits

3.15 The committee considered whether there were any uncaptured benefits of quizartinib. It noted that quizartinib was the first treatment specifically targeted to the FLT3-ITD mutation, but it did not identify additional benefits of quizartinib not captured in the economic modelling. So, the committee concluded that all additional benefits of quizartinib had already been taken into account.

## Conclusion

### Recommendation

- 3.16 The range of ICERs that the committee considered to be plausible was below £20,000 per QALY gained. So, the committee recommended quizartinib for newly diagnosed FLT3-ITD-positive AML.

## 4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has newly diagnosed FLT3-ITD-positive acute myeloid leukaemia (AML) and the healthcare professional responsible for their care thinks that quizartinib is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Evaluation committee members and NICE project team

## Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

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

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

## Chair

**Stephen O'Brien**

Chair, technology appraisal committee C

## NICE project team

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

**Kirsty Pitt**

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