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External Assessment Group Report

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

EAG addendum: review of time on treatment scenario

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The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all depersonalised data (DPD) [redacted]

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1 OVERVIEW

As part of the company's factual accuracy check (FAC), the company provided additional analysis addressing concerns raised in the evidence assessment report (EAR) regarding how drug acquisition, administration and monitoring costs were estimated in the company's base case analysis model. Details of this critique are presented in Section 4.4.2 of the EAR.

The scenario analysis presented by the company attempts to implement the Evidence Assessment Group's (EAG) proposed methodology for estimating time on treatment (ToT) described in Table 26 of EAR. The company further updates how relative dose intensity (RDI) is applied in the economic analysis to use a phased approach. The company are clear that this analysis is presented for exploratory purposes only. The company continues to consider the approach applied in the company base case appropriate. The company does not offer any justification for this preference, nor does it offer any critique of the EAG's proposed approach.

1.1 EAG comment

A requirement of the EAG preferred approach to modelling ToT is that the ToT curves should be censored for relapse, haematopoietic stem cell transplantation (HSCT) and death events. However, the company's description of the scenario analysis does not clarify whether the ToT curves used in the model have been appropriately censored. The EAG assumes that this censoring has been performed, and the presented analysis aims to fully replicate the EAG's outlined methodology, though this cannot be verified by the EAG.

1.2 Implementation issues

The EAG notes several issues with how the additional ToT scenarios has been implemented in the economic model.

Firstly, the company has applied consolidation treatment administration and monitoring costs only to patients who enter the CR 1L health state. This is incorrect; these costs should apply to patients entering both the CR 1L and HSCT 1L health states, reflecting the fact that patients can receive consolidation treatment before proceeding to HSCT. On this point, the EAG emphasises that its approach to modelling ToT is designed to work in combination with other corrections made to the model regarding the timing of HSCT. The EAG is aware that these corrections make some abstractions from reality but are done with the intention of making the model calculations simpler. Failure to accept these corrections will result in miscalculated drug acquisition, administration, and monitoring costs.

Secondly, the company assumes patients will receive 14, not 12, cycles of maintenance treatment. This appears to be a transcription error, given the description of the scenario provided by the company.

Thirdly, in patients who do not receive HSCT, the company refers to the wrong cells and left truncates the ToT curve so that it starts at cycle 1 rather than cycle 0. This is likely a calculation error as this has been implemented correctly for patients who receive HSCT.

The EAG addresses and corrects these issues in further scenario analyses presented in Section 2.

C*ompliance quizartinib maintenance regimen*

The updated scenario provides further evidence on the rate of treatment discontinuations for patients receiving maintenance phase treatment with quizartinib. The ToT data included in the economic model indicates that discontinuation rates are relatively high, and few patients who remain disease-free (i.e. are alive and have not relapsed) complete the full 36 cycles of maintenance treatment (see Table 1). Furthermore, RDI for the maintenance phase is relatively low, at [redacted], suggesting poor compliance with the quizartinib maintenance regimen. The reasons for this poor compliance are unclear and may indicate issues of tolerability or simply reflect patient preference.

In terms of the economic analysis, this poor compliance with the quizartinib maintenance regimen results in substantially lower drug acquisition and monitoring costs than if patients adhered more closely to the recommended posology. For instance, the mean time on maintenance treatment following HSCT is only [redacted] months, significantly less than the 36 months specified in the summary of product characteristics (SmPC). It is therefore important to consider whether the discontinuation and dose compliance rates observed in the QuANTUM-First trial will be replicated in the NHS. If not, drug acquisition and administration costs may be significantly higher than those captured by the model.

Table 1 Landmark analysis of time on quizartinib maintenance treatment

	Maintenance treatment without HSCT	Maintenance treatment with HSCT
Percentage receiving 12 cycles or more*	[redacted]	[redacted]
Percentage receiving 24 cycles or more*	[redacted]	[redacted]
Percentage receiving 36 cycles or more*	[redacted]	[redacted]

* Percentages are conditional on patients remaining alive and relapse-free

2 ADDITIONAL SCENARIO ANALYSIS

Table 2 presents the result of the company's additional scenario analysis applied to the EAG base case. These results replicated those provided by the company and include corrections to the EAG base case made as part of the FAC but do not address the points raised in Section 1.2. The corrected results are presented in Table 2 and make the following changes to the model:

- Consolidation drug acquisition, administration and monitoring costs are applied (lump sum) on entry to both the CR 1L and HSCT 1L health states.
- The maximum number of cycles of midostaurin is capped at 12 (in line with the SmPC).
- Time on treatment for patients who don't receive HSCT is shifted to start at time zero.

All results presented in this Section include the PAS discount for quizartinib but exclude commercial arrangements for the comparator treatments. Results inclusive of available commercial arrangements for the comparator treatments are provided in a confidential appendix to this report.

The EAG considered the correct scenario analysis to largely resolve the issues discussed in Section 4.4.2 of the EAR. The 4th analysis presented in Table 2 (inclusive of both changes to ToT and RDI) therefore reflects the EAG's new base case.

Table 2 EAG's preferred approach to modelling time on treatment and RDI and new EAG base case

Scenario	Technology	Total		Incremental		Fully incremental ICER	Pairwise ICER vs SC
		Costs	QALYs	Costs	QALYs		
EAG base case	SC regimen	[redacted]	[redacted]				
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£133,861	£133,861
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,288	£52,519
EAG base case plus company's implementation of EAG preferred approach to ToT	SC regimen	[redacted]	[redacted]				
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£158,839	£158,839
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£18,494	£60,909
EAG base case plus company's implementation of EAG preferred approach to ToT plus RDI applied by treatment phase	SC regimen	[redacted]	[redacted]				
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£158,839	£158,839
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,247	£55,155
New EAG base case: EAG base case plus	SC regimen	[redacted]	[redacted]				

corrected EAG preferred approach to ToT plus RDI applied by treatment phase	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£163,476	£163,476
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£12,863	£58,382

Abbreviations: EAG: Evidence assessment group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-years; RDI: relative dose intensity; SC, standard chemotherapy; ToT: time on treatment.