Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Daiichi Sankyo:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Clarification response – questions A9 and B9
   c. Clarification response – questions A15 and B12
   d. Clarification response – question B12a

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Blood Cancer UK
   b. Leukaemia Care
   c. Royal College of Pathologists

4. **Expert personal perspectives** from:
   a. Dr Priyanka Mehta – clinical expert, nominated by Daiichi Sankyo
   b. Professor Steven Knapper – clinical expert, nominated by Leukaemia Care
   c. Esther Beswick – patient expert, nominated by Leukaemia Care

5. **External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York
   a. External Assessment Report
   b. EAG post-FAC addendum
   c. Additional EAG analyses

6. **External Assessment Report – factual accuracy check**

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

Single technology appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Document B

Company evidence submission

March 2024

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Contents

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List of abbreviations

Abbreviation	Definition
Admin	Administration route
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
AKT	Protein kinase B
ALL	Acute lymphoblastic leukaemia
HSCT	Hematopoietic stem cell transplantation (allogeneic)
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukaemia
AR	Allelic ratio
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
ATRA	All-trans retinoic acid
AZCERT	The Arizona Center for Education and Research on Therapeutics
BIC	Bayesian information criterion
BMI	Body mass index
BMJ	British Medical Journal
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
C	Cycle
CC	Complication/comorbidity
CDSR	Cochrane Database of Systematic Reviews
CE	European conformity
CEBPA	CCAAT enhancer-binding protein alpha
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CHEMO	Chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIR	Cumulative incidence of relapse
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CR	Complete remission
CRc	Composite complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete neutrophil or platelet recovery
CRO	Contract research organization
CR1	First CR
CR2	Second CR
CS	Company's submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
D	Day
DCO	Data cut-off

Abbreviation	Definition
DNA	Deoxyribonucleic acid
DFS	Disease-free survival
DoCR	Duration of complete remission
DOF	Data on file
DS	Daiichi Sankyo
DSU	Decision Support Unit
EAG	External assessment group
EC	Ethics Committee
EC	European commission
ECG	Electrocardiogram
ECM	Established clinical management
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
EMD	Extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer core quality of life questionnaire
EQ-5D-5L	EuroQoL-5D-5L
ER	Emergency room
ERG	Evidence review group
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
ESS	Estimated sample size
FDA	United States Food and Drug Administration
FLAG-Ida	Fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor
FLT3	FMS-like tyrosine kinase 3 (refers to the protein)
FLT3	FMS-like tyrosine kinase 3 (refers to the gene)
FLT3+	FMS-like tyrosine kinase 3 positive
FLT3i	FMS-like tyrosine kinase 3 inhibitor
FLT3-ITD	FMS-like tyrosine kinase 3 internal tandem duplication
FLT3-ITD+	FMS-like tyrosine kinase 3 internal tandem duplication positive
FMS	Feline McDonough sarcoma
GBP	Great British Pound
GVHD	Graft-vs.-host disease
HCRU	Healthcare resource utilisation
HEOR	Health economics and outcomes research
HiDAC	High-dose cytarabine
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplantation
HSE	Health and Safety Executive
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICU	Intensive care unit
ICUR	Incremental cost-utility ratio
IDAC	Intermediate-dose cytarabine

Abbreviation	Definition
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
IQR	Interquartile range
IRB	Institutional Review Board
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITD	Internal tandem duplication
ITF	Induction treatment failure
ITT	Intent-to-treat
IV	Intravenous
JAK	Janus kinase
KI	Kinase insert
KM	Kaplan-Meier
LDAC	Low-dose cytarabine
LR	Log-rank
LVEF	Left ventricular ejection fraction
MAIC	Matching adjusted treatment indirect comparison
MCID	Minimal clinically important difference
MDS	Myelodysplastic syndrome
MEC	Mitoxantrone, etoposide and cytarabine
MEK	Mitogen-activated protein kinase
MHRA	Medicines and Healthcare products Regulatory Agency
MIDO	Midostaurin
MLFS	Morphologic leukaemia-free state;
MMRM	Mixed-effects model for repeated measures
MPN	Myeloproliferative neoplasm
MRD	Minimal or measurable residual disease
ms	Millisecond
MUGA	Multi-gated acquisition scan
NA	Not applicable
NCCN	National Comprehensive Cancer Network
ND	Newly diagnosed
NE	Not estimable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIHR iCT	National Institute for Health and Care Research, interactive costing tool
NMR	Net monetary benefit
NPM1	Nucleophosmin 1
NR	Not reported
NYHA	New York Heart Classification
ONS	Office for National Statistics
OR	Odds ratio
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PBO	Placebo
PH	Proportional hazards
PIA	Plasma inhibitory assay
PI3K	Phospatidylinositol-3-kinase

Abbreviation	Definition
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
QT	Interval between the start of the Q wave and the end of the T wave
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
QUIZ	Quizartinib
Qz	Quizartinib
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RFS	Relapse-free survival
RMST	Restricted mean survival time
RNA	Ribonucleic acid
R/R	Relapsed/refractory
RTK	Receptor tyrosine kinase
Relapse1	First relapse
Relapse2	Second relapse
SAE	Serious adverse event
SC	Standard chemotherapy
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
STAT5a	Signal transducer and activator transcription factor 5a
TA	Technology appraisal
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
TKD	Tyrosine kinase domain (refers to the protein)
TKD	Tyrosine kinase domain (refers to the gene)
TM	transmembrane domain
TP	Transition probability
TSD	Technical support document
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAF	Variant allele frequency
VAS	Visual analogue scale
VAT	Value added tax
WBC	White blood cell
WHO	World Health Organization
WTP	Willingness-to-pay

Abbreviation	Definition
1L	First-line treatment
2L	Second-line treatment

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Quizartinib (VANFLYTA®, Daiichi Sankyo United Kingdom [UK] Ltd.) has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 15th of September 2023 and European Medicines agency (EMA) approval was received on the 6th of November 2023. A market authorisation application for quizartinib was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) on the 22nd of September 2023 and a decision is expected within the second quarter of 2024 for the same indication:

- Quizartinib is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is Feline McDonough sarcoma (FMS)-like tyrosine kinase 3 internal tandem duplication positive (*FLT3-ITD+*) (1).

This submission covers the full anticipated marketing authorisation as above. The decision problem addressed within this submission is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with newly diagnosed AML that is *FLT3-ITD+*	Aligned with NICE scope	NA
Intervention	Quizartinib	Aligned with NICE scope **Quizartinib regimen:** • **Induction phase**: Quizartinib + chemotherapy (daunorubicin or idarubicin + cytarabine) • **Consolidation phase**: Quizartinib + chemotherapy (cytarabine) • **Maintenance phase**: quizartinib single agent maintenance therapy for patients who achieve CR (with or without HSCT)	NA
Comparator(s)	**Induction phase:** • Established clinical management without quizartinib, including but not limited to midostaurin with daunorubicin and cytarabine. **Consolidation phase:** • Established clinical management without quizartinib, including but not limited to midostaurin with cytarabine alone or in combination with other chemotherapy drugs, such as mitoxantrone, etoposide, or amsacrine.	**Midostaurin regimen:** • **Induction phase**: Midostaurin + chemotherapy (daunorubicin + cytarabine) • **Consolidation phase**: Midostaurin + chemotherapy (cytarabine) • **Maintenance phase**: Midostaurin single agent maintenance therapy for patients who achieve CR but did not receive HSCT.	**The non-routine chemotherapy treatments (mitoxantrone, etoposide, amsacrine) were not considered as appropriate comparators for the newly diagnosed AML patients with *FLT3-ITD+*** • There is no NICE guidance supporting the use of these treatments in AML in first line • These examples do not feature in the clinical guidelines supporting the scope (2). These therapies are recommended, in the reference provided by NICE in the scope (2), to be used in 'younger patients with adverse-risk

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Maintenance phase: • Established clinical management without quizartinib including but not limited to midostaurin and azacitidine	**SC regimen:** • **Induction phase**: Chemotherapy (daunorubicin or idarubicin + cytarabine) • **Consolidation phase**: Chemotherapy (cytarabine) • **Maintenance phase**: No maintenance treatment.	cytogenetics…if there are delays to planned HSCT or if patients are not fit for allograft' • There is limited evidence to demonstrate the benefits of using these therapies in *FLT3-ITD*+ patients. The recommendations referenced by NICE in the scope (2, 3) are based on the Burnett et al., 2013 and Burnett et al., 2010 trials, which both enrolled a broader AML population with a low proportion of *FLT3-ITD*+ patients (9-29%) (4, 5) • No precedence has been identified for the specification of non-routine chemotherapy drugs in prior NICE scopes in this indication, most notably with reference to TA523 (midostaurin) (6). **Azacitidine is not considered an** appropriate comparator because of the following: • TA827 (azacitidine) states that *'some people with FLT3-mutation-positive AML can have targeted maintenance treatment with midostaurin. Therefore, oral azacitidine would likely be of most benefit to people whose AML does not have an FLT3-mutation'* (7) • Azacitidine is not specific for the *FLT3*-mutation. The European LeukemiaNet (ELN) 2022 guideline does not recognise

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			azacitidine as standard treatment in the FLT3+ population, who should be treated with targeted therapy (8) • Azacitidine is only licenced for people not eligible for HSCT in the UK (9). However, quizartinib is suitable in the consolidation/maintenance phase for patients who received quizartinib and intensive chemotherapy regardless of their subsequent eligibility for HSCT • While it is possible that azacitidine may be used in clinical practice after midostaurin in *FLT3+* patients who did not receive HSCT due to a lack of treatment options, such use is not supported by clinical trial data, clinical expert opinion or the identified AML guidelines (8, 10) • In addition, the clinical trial of azacitidine begins at the maintenance phase and uses various treatments (not including quizartinib or midostaurin) in the induction and consolidation phases (11). Consequently, any indirect treatment comparison (ITC) conducted using this trial to compare azacitidine with quizartinib and midostaurin would entail significant uncertainty. • UK clinical experts in an advisory board (AdBoard) concluded that azacitidine is not considered as a relevant comparator in the maintenance phase as it is not a

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			treatment that would be used in clinical practice with *FLT3* patients. Including azacitidine as a comparator in the model may therefore be problematic (12).
Outcomes	The outcome measures to be considered include: • Overall survival • Event-free survival • Relapse-free survival • Adverse effects of treatment • Health-related quality of life.	The outcome measures to be considered include: • Overall survival • Event-free survival • Relapse-free survival • Adverse effects of treatment • Health-related quality of life • Complete remission • Duration of complete remission • Transplantation rate.	• Consistent with TA523 and the endpoints collected in the QuANTUM-First trial, complete remission, duration of complete remission, and transplantation rate were also considered relevant outcomes.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently	Aligned with NICE scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	People who are ineligible for HSCT	No subgroup was considered.	Based on the QuANTUM-First protocol, all patients enrolled in the trial were eligible for intensive chemotherapy where the ultimate therapeutic goal is HSCT. Therefore, a subgroup analysis of people ineligible for HSCT was not a pre-specified subgroup and such analysis could not be conducted due to the trial design (13).
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	NA	NA

Abbreviations: HSCT, hematopoietic stem cell transplantation, AML, acute myeloid leukaemia; CR, complete remission; *FLT3-ITD+*, FMS-like tyrosine kinase 3 internal tandem duplication positive; HSCT, hematopoietic stem cell transplantation; ITC, indirect treatment comparison; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SC, standard chemotherapy; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

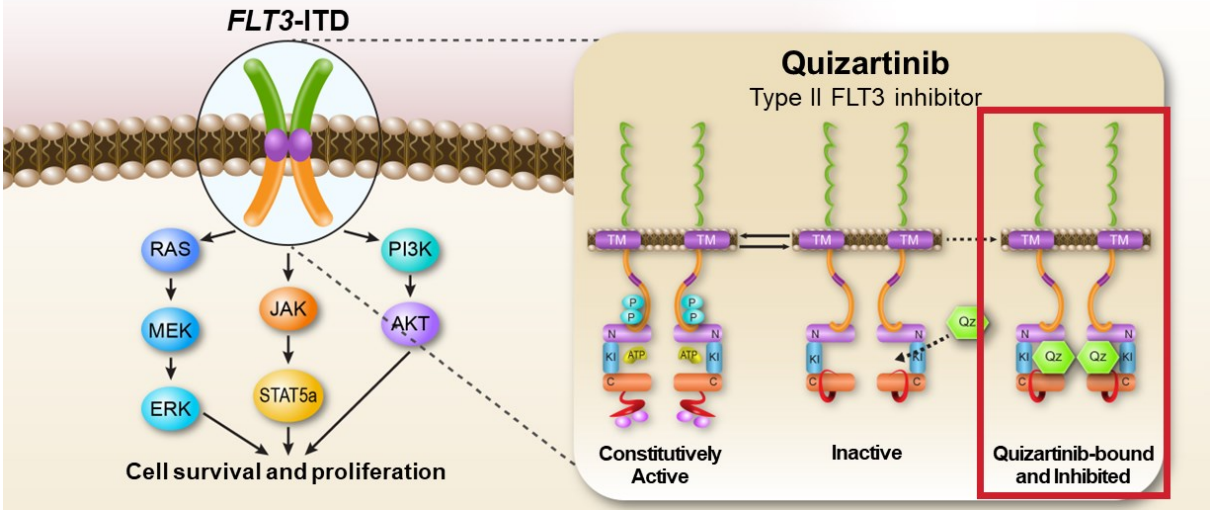
B.1.2.1 Mechanism of action

Quizartinib is a novel oral small molecule receptor tyrosine kinase (RTK) inhibitor exhibiting highly potent and selective inhibition of FMS-like tyrosine kinase 3 (FLT3) signalling (14). It is a second-generation, type II FLT3 inhibitor, targeting FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3-ITD*) (15).

FLT3 is a transmembrane ligand-activated RTK that is expressed by haematopoietic stem or progenitor cells. Extracellular FLT3 ligands bind and activate FLT3, promoting cell survival, proliferation and differentiation (16). In normal bone marrow FLT3 plays an important role in the early stages of both myeloid and lymphoid lineage development (16, 17).

FLT3-ITD mutations occur in the juxtamembrane domain of the cell (18) and result in a conformational change in the receptor from an inactive to a constitutively active state, even in the absence of the FLT3 ligand (Figure 1) (16, 17). This results in the proliferation and survival of AML (16).

Figure 1. Quizartinib mechanism of action



Abbreviations: AKT, protein kinase B; ATP, adenosine triphosphate; C, C-lobe; ERK, extracellular signal-regulated kinase; FLT3, FMS-like tyrosine kinase 3; *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; JAK, janus kinase; KI, kinase insert; MEK, mitogen-activated protein kinase; N, N-lobe, TK1 domain; nM, nanomolar; P, phosphorylation site; PI3K, phospatidylinositol-3-kinase; PIA, plasma inhibitory assay; Qz, quizartinib; RAS, rat sarcoma; STAT5a, signal transducer and activator transcription factor 5a; TM, transmembrane domain.
Reference: figure adapted with permission from Grafone et al., 2012 (17).

Quizartinib and its major metabolite, AC886, competitively bind to the adenosine triphosphate (ATP) binding pocket of FLT3 in its inactive conformation with high affinity (dissociation constant =1.3 nM) and maintain the receptor in this inactive conformation (16, 19). This prevents autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking *FLT3-ITD* dependent cell proliferation. These features lead to the classification as a type II inhibitor, as type I inhibitors bind to the ATP binding pocket in its active conformation (20).

Quizartinib has shown significant inhibition of FLT3 phosphorylation at concentrations of 0.8 to 20 nM (in human MV4 11 cell line, which harbours the *FLT3-ITD* mutation commonly found in AML), indicating that the compound is a highly potent intracellular inhibitor of *FLT3-ITD* kinase activity (19) and it has been found to be more potent in vivo than any other FLT3 inhibitor to date (21). The selectivity of quizartinib and AC886 has been demonstrated by their lower binding affinity to receptor tyrosine kinase c-KIT (19). This selectivity of quizartinib, is another feature of being a second-generation inhibitor (22). It is thought that limiting off-target effects, could reduce the drug toxicity and adverse effects to patients associated with first-generation inhibitors.

B.1.2.2 Technology being appraised

The main characteristics of quizartinib are summarised in Table 2. For the full summary of product characteristics (SmPC), see Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Quizartinib, (VANFLYTA®)
Mechanism of action	Quizartinib is an inhibitor of the receptor tyrosine kinase FLT3. For a detailed overview of mechanism of action, see section B.1.2.1.
Marketing authorisation/CE mark status	• CHMP positive opinion from the CHMP: 15th of September 2023 • EC decision/EMA approval on the 6th of November 2023. A market authorisation application for quizartinib was submitted to the MHRA on the 22nd of September 2023 and a decision is expected within the second quarter of 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Proposed indication:** Quizartinib is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib single agent maintenance therapy for adult patients with newly diagnosed AML that is *FLT3-ITD+.* **Contraindications:**

<table>
<tr><td></td><td>

Hypersensitivity to the active substance or to any of the excipients
Congenital long QT syndrome
Breast-feeding.

For the full draft SmPC, see Appendix C.
</td></tr>
<tr><td>Method of administration and dosage[a]</td><td>
Method of administration: Oral.

Dosage forms and strengths
Quizartinib is supplied as film-coated tablets containing 17.7 mg or 26.5 mg of quizartinib, which are equivalent to 20 mg and 30 mg quizartinib dihydrochloride, respectively.

Dose regimen
<table>
<tr><td rowspan="2">Quizartinib initiation</td><td>Induction [a]</td><td>Consolidation [b]</td><td>Maintenance</td></tr>
<tr><td>Starting on day 8 (For 7 + 3 regimen) [c]</td><td>Starting on day 6</td><td>First day of maintenance therapy</td></tr>
<tr><td>Dose</td><td>35.4 mg once daily</td><td>35.4 mg once daily</td><td>• Starting dose of 26.5 mg once daily for two weeks if QTcF is ≤ 450 ms.
• After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg once daily.</td></tr>
<tr><td>Duration (28-day cycles)</td><td>Two weeks in each cycle</td><td>Two weeks in each cycle</td><td>Once daily with no break between cycles for up to 36 cycles.</td></tr>
</table>
[a] Patients can receive up to 2 cycles of induction.
[b] Patients can receive up to 4 cycles of consolidation.
[c] For the 5 + 2 regimen as the second induction cycle, quizartinib will be started on day 6.

For patients who proceed to HSCT
Quizartinib should be stopped seven days before the start of a conditioning regimen. Quizartinib may be resumed after completion of the transplant based on WBC and at the discretion of the treating physician for patients with sufficient haematologic recovery and with ≤ Grade 2 GVHD, not requiring the initiation of new systemic GVHD therapy within 21 days.

Dose modifications
Quizartinib should be initiated only if QTcF is ≤ 450 ms. The dose modifications and adjustments due to adverse reactions and/or concomitant use with strong CYP3A inhibitors are implemented. Further details including dose modifications are available in the SmPC, see Appendix C.
</td></tr>
<tr><td>Additional tests or investigations</td><td>

FLT3-ITD mutation testing, which is already routine in NHS practice (2).
During induction and consolidation, ECGs should be performed prior to initiation and then once weekly during quizartinib treatment or more frequently as clinically indicated. During maintenance, ECGs should be performed prior to initiation and then once weekly for the first month following dose initiation and escalation, and thereafter as clinically indicated. The maintenance starting dose should not be escalated if the QTcF

</td></tr>
</table>

	interval is greater than 450 ms. ECG monitoring of the QT interval should be performed more frequently in patients who are at significant risk of developing QT interval prolongation and Torsades de Pointes. Patients should be monitored more frequently with ECG if co-administration of quizartinib with medicinal products known to prolong the QT interval is required • Monitoring and correction of hypokalaemia and hypomagnesaemia should be performed prior to and during treatment with quizartinib. More frequent monitoring of electrolytes and ECGs should be performed in patients who experience diarrhoea or vomiting. Additional tests or investigations has been incorporated in the economic analyses.
List price and average cost of a course of treatment[a]	Proposed list prices (excluding VAT) as follows: • Quizartinib 17.7 mg base (equivalent to 20mg quizartinib dihydrochloride) x 28 tablets: [redacted] • Quizartinib 26.5 mg base (equivalent to 30mg quizartinib dihydrochloride) x 56 tablets: [redacted] The average modelled cost of a course of treatment at the list price is [redacted] (This is based on the company's CEM undiscounted outcomes in Section B3, which include the costs of quizartinib in the induction, consolidation and maintenance phases)
Patient access scheme (if applicable)	Daiichi Sankyo UK has an approved Patient Access Scheme (PAS). The proposed PAS fixed price per pack (excluding VAT) is [redacted] for 28 x 17.7 mg tablets and [redacted] for 56 x 26.5 mg tablets. This equates to a discount on the NHS list price of [redacted]. The average modelled cost of a course of treatment at the PAS price is [redacted] (This is based on the company's CEM undiscounted outcomes in Section B3, which include the costs of quizartinib in the induction, consolidation and maintenance phases)

Abbreviations: AML, acute myeloid leukaemia; CE, European conformity; CHMP, Committee for Medicinal Products for Human Use; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; EC, European commission; ECG, electrocardiogram; EMA, European Medicines Agency; FLT3, FMS-like tyrosine kinase 3; *FLT3-ITD+*, FMS-like tyrosine kinase 3 internal tandem duplication positive; GVHD, graft-vs.-host disease; HSCT, haematopoietic stem cell transplantation; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; QT, interval between the start of the Q wave and the end of the T wave; QTcF, QT interval corrected by Fridericia's formula; SmPC, summary of product characteristics; UK, United Kingdom; VAT, value added tax; WBC, white blood cell.

References: Daiichi Sankyo, 2023 (1).
Notes: a. Vanflyta is manufactured in the dihydrochloride salt form of the drug. 17.7 mg and 26.5 mg of quizartinib base are equivalent to 20 mg and 30 mg, of quizartinib dihydrochloride respectively.

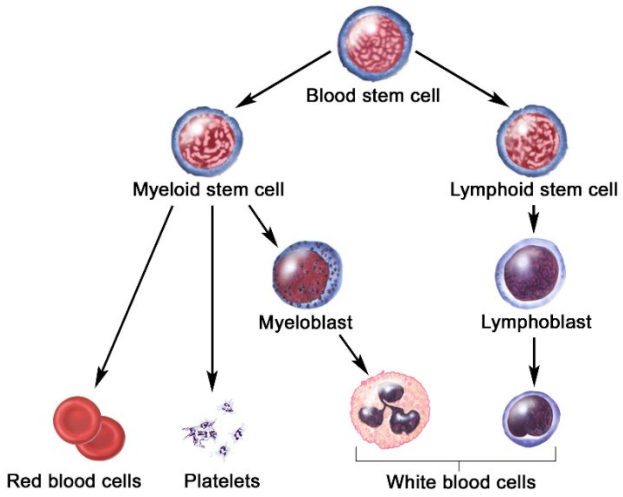
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Description of acute myeloid leukaemia

AML is a rapidly progressing cancer of the blood and bone marrow (23-25). In healthy individuals, haematopoietic stem cells (myeloid and lymphoid stem cells) mature and differentiate into functioning red blood cells, platelets and white blood cells; this process is referred to as haematopoiesis (Figure 2) (24).

Figure 2. Diagram of the cell lineage of haematopoiesis



Reference: National Cancer Institute, 2022 (24)

In AML, the myeloid stem cells become a type of immature white blood cell (WBC) called myeloblasts. These myeloblasts are abnormal and do not become healthy WBCs. Normal WBCs are therefore replaced by leukaemic cells that have a diminished ability to defend against infection (26). The rapid proliferation of abnormal myeloblasts, as well as the reduction of apoptosis (programmed cell death) of these abnormal cells, results in the accumulation of abnormal myeloblasts in the bone marrow, blood and often the liver and spleen (27). The accumulation of these immature, abnormal myeloblasts leads to the decreased production of normal blood cells resulting in anaemia, thrombocytopenia and neutropenia (27).

AML is a heterogeneous malignancy characterised by chromosomal abnormalities, recurrent gene mutations, epigenetic modifications and microribonucleic acid

deregulation (28). The *FLT3* gene encodes a tyrosine kinase receptor, which plays a key role in haematopoiesis as described in section B.1.2.1 (4). There are two characterised types of *FLT3* mutations: *FLT3-ITD* and point mutations or deletion in the tyrosine kinase domain (TKD). The *FLT3-ITD* mutation is more common being found in 20% to 25% of AML than the *FLT3-TKD* mutation, which is found in 7% to 10% of all AML cases (29). The *FLT3-ITD* mutation leads to constitutive activation of the tyrosine kinase receptor and downstream signalling through multiple kinases (rat sarcoma [RAS] / rapidly accelerated fibrosarcoma [RAF] kinase / mitogen activated protein kinase [MEK] / extracellular signal regulated kinase [ERK]), signal transducer and activator of transcription 5 (STAT5) and phosphoinositide 3-kinases (PI3-kinases) (30). According to the 2022 European Leukaemia Network (ELN) guidelines, the *FLT3-ITD* mutation is a poor prognosis factor and its presence, unlike the *TKD* mutation, leads to an intermediate risk classification (8).

Clinical presentation

The majority of clinical manifestations of AML are related to the accumulation of malignant, poorly differentiated myeloid cells within the bone marrow, peripheral blood, and (less commonly) other organs (23). AML can arise in patients with an underlying haematological disorder, or as a consequence of prior therapy (for example, exposure to topoisomerases II, alkylating agents or radiation) (23). However, in the majority of cases, it appears as a de novo malignancy in previously healthy individuals (23). Patients typically present with an array of symptoms that can include fatigue, fever, infections, breathlessness, and bruising, which usually develop four to six weeks before diagnosis, increase in severity over time and prompt testing (24, 31). Clinical presentation commonly includes a combination of leucocytosis (i.e., abnormally high levels of WBC) and signs of bone marrow failure, such as anaemia and thrombocytopenia (23). Serious, potentially life-threating complications of AML include uncontrolled infections; bleeding in the lungs, gastrointestinal tract and central nervous system; and leukostasis (a medical emergency associated with respiratory distress and altered mental status) (26, 32). If left untreated, AML progresses rapidly, and death may occur within months of diagnosis secondary to infection or bleeding (23).

B.1.3.2 Epidemiology

AML is the most common acute leukaemia in adults (33, 34). The crude incidence rate of AML cases per year from 2016-2018 in the UK was 4.7 cases per 100,000 persons (35). Incidence of AML increases with age, with over 70% of new cases being in those over 60 years of age and more than 4 in 10 new cases (42%) in the period between 2016-2018 being in those above 75 years of age (35). Since elderly individuals are at a higher risk of developing AML, an aging population may be contributing to the increasing AML incidence rates observed in the UK (35-38). Over the past several decades AML incidence has generally been increasing, with the age-standardised incidence rate in the UK increasing by 20% between 1993-1995 and 2016-2018 (35).

FLT3 is one of the most common AML mutations (39, 40). The *FLT3-ITD* mutation is especially prevalent being found in 20% to 25% of AML patients (16, 28) whereas the *FLT3-TKD* mutation is only present in 7% to 10% of patients (29). This is reaffirmed in a UK-specific study where approximately 27% of patients with AML (*de novo* or secondary) tested positive for the *FLT3-ITD* mutation (41). The presence of the *FLT3-ITD* mutation is linked to several demographic factors, with higher incidence in females and younger patients (29).

B.1.3.3 Disease burden

Clinical burden

AML is an aggressive cancer, associated with rapid progression and poor survival outcomes (23). In England alone the average annual number of deaths from AML between 2017 and 2019 was 2,255 (35). Men died more frequently, with an average of 1,328 deaths vs. 927 deaths for women. Since the 1990s the incidence of AML has increased by 20% in the UK. This could be linked to an aging population (see B.1.3.2). Although the AML mortality rate in the UK has remained stable over the last decade, the increase in incidence has led to an increase in mortality rates of 55% since the 1970s (35). Beyond an increased risk of mortality, it has also been found that patients with AML suffer from higher rates of comorbidities, specifically heart disease, than matched non-cancer patients (42).

Clinical outcomes of AML are largely dependent on a range of prognostic factors. These include patient-specific factors such as age, gender, Eastern Cooperative

Oncology Group (ECOG) performance status, organ function and other comorbidities (43). Equally significant are disease-specific factors such as cytogenetic and/or molecular alterations, which include *FLT3* and nucleophosmin 1 (*NPM1*) mutations. In regard to haematological status, ELN and ESMO guidelines both consider CRi as positive response to treatment (8, 44).

In particular, the *FLT3-ITD* mutation has been reported to be associated with poorer clinical outcomes with higher rates of relapse and lower rates of disease-free survival (DFS), event-free survival (EFS) and overall survival (OS) compared to *FLT3-TKD* patients (41, 45-47). This can be linked to the high leukaemic burden faced by *FLT3-ITD* patients, with higher WBC counts and more blasts in the peripheral blood and bone marrow at diagnosis than AML patients without the mutation (41).

The increased risk of mortality was shown in a meta-analysis by Liu et al., (2020) (45), which covered 13 countries including the UK. Patients with the *FLT3-ITD* mutation, when compared to those without the *FLT3-ITD* mutation, had an OS hazard ratio (HR) of 1.86 (95% confidence interval [CI]: 1.30, 2.39; P<0.001) in those with the *NPM1* mutation and 1.94 (95% CI: 1,39, 2.03; P<0.001) in those without the *NPM1* mutation. OS outcomes can be improved with allogeneic haematopoietic stem cell transplant (HSCT), however, patients with *FLT3-ITD* still face a high risk of relapse even after the transplant (2-year relapse incidence: 30% vs. 16%) (48). This increased risk is reflected in the 2022 ELN risk classification, where a *FLT3-ITD* mutation alone warrants the intermediate risk category (8).

Humanistic burden

Compared to the general population, patients with AML are faced with lower health related quality of life (HRQoL) (49, 50). HRQoL is especially impacted following diagnosis and the initiation of treatment (51). Improvements are seen for patients that undergo successful treatment and are considered survivors, with some functional domains almost returning to levels of the general population (51).

The importance of health state and treatment modality on HRQoL was demonstrated in three UK studies (52-54). Using the time trade-off method, the utility of AML health states was determined. Although the health states included in these three studies

varied, it was shown that diagnosis and treatment initiation were associated with lower utility compared with remission and cure health state. Relapse and stem cell transplant (SCT) had particularly low utility with Castejon et al., (2018) (52) reporting a utility value of 0.1 for relapse and Joshi et al., (2019) (53) attributing a utility value of -0.21 for SCT. For SCT, however, recovery and long-term follow-up without complications showed significant utility improvement with values of 0.75 and 0.94, respectively.

Limited evidence on the HRQoL specifically for *FLT3-ITD* patients is available, however, it is suggested that these patients have worse HRQoL than those without this mutation. One study of limited sample size by Horvath Walsh et al., (2019) (55) examined the HRQoL of 54 AML patients, with seven of these having the *FLT3-ITD* mutation. The EQ-5D utility score for AML patients was 0.64 vs. 0.76 for patients with and without the *FLT3-ITD* mutation, respectively.

Economic burden

Economic burden, including costs and healthcare resource utilisation (HCRU), is substantial among patients with newly diagnosed AML with evidence demonstrating that hospitalisations and stem cell transplantation are major contributors to costs (56, 57).

In the UK, it was estimated that the annual economic burden associated with the direct treatment of AML is more than £50 million, with £13 million for the population older than 65 years and £38 million for the population under 65 years (57). This total burden was calculated by combining the frequency and cost of standard management of AML per patient in the UK and UK-specific incidence data. The per-patient cost is estimated to be £37,746 for patients receiving induction chemotherapy and consolidation only and £112,545 for patients also receiving HSCT (58).

This high economic burden is driven by HCRU. National Institute for Health and Care Excellence (NICE) TA523 (6), which examined the treatment of newly diagnosed *FLT3+* AML patients with midostaurin, provides estimates of HCRU in the UK by health state. In induction it is estimated that per cycle, patients spend 66 minutes with a clinical nurse specialist, 62 minutes with a consultant, 139 minutes with a junior doctor and 12,290 minutes in inpatient days. This list is not exclusive with more time being

spent on pharmacists, oncology nurses and other health care professionals. Focusing on inpatient days, which are considered large cost drivers, patients are expected to spend 12,290 minutes when in second induction, 828 minutes when in consolidation and monotherapy/complete remission and 5,702 minutes when in relapse.

UK-specific economic burden data is relatively limited. However, the findings of two multi-country studies (59, 60), which included the UK, but did not report findings by country, (59, 60) aligned with NICE TA523 (6) and demonstrated high HCRU for newly diagnosed AML patients.

For patients with newly diagnosed AML, HCRU was increased during relapse or treatment failure compared with the period prior to relapse or failure. This included average inpatient admissions per month (0.52 vs 0.27), inpatient stays per month (6.5 vs 5.4 days), intensive care unit (ICU) days per month (0.5 vs 0.28 days) and emergency room (ER) visits per month (0.54 vs 0.23) (59). These results were based on a medical chart review of patients with AML from 10 countries (United States [US], Canada, UK, France, Germany, Spain, Italy, Netherlands, Japan and South Korea).

Data pertaining to newly diagnosed *FLT3*-mutated AML patients is limited, however it was found that it is associated with four times more inpatient admissions (P = 0.0045), higher rates of ICU admissions (P = 0.0003) and higher rates of ER visits (P = 0.0005) compared with *FLT3*-wild type AML, based on a retrospective chart review of patients with AML performed in Canada, the UK, France, Germany, Italy and Spain from January 2017 to March 2020 (60).

B.1.3.4 Current treatment guidelines

Currently the ELN guidelines, published in 2022, are recognised as the main guidelines followed for the management of AML in the UK (8). Other regional guidelines include the National Health Service (NHS) Pan-London guidelines and the 2020 European Society for Medical Oncology (ESMO) guidelines (2, 44, 61, 62).

Diagnosis

The diagnosis of AML is typically made on the basis of a combination of factors including a complete blood count and differential count, bone marrow aspirate, bone

marrow trephine biopsy and immunophenotyping (8). According to the ELN guidelines, the Pan-London guidelines, and the ESMO guidelines, cytogenetic and molecular genetic testing should be performed at diagnosis for genetic abnormalities including *FLT3* mutations to guide clinical decisions and predict prognosis (2, 8, 44). These guidelines all recommend that testing should be carried out immediately after diagnosis (6). This allows timely initiation of therapy with a FLT3 inhibitor (6).

Recently (2022), ELN have developed recommendations for risk stratification that categorise risk according to the genetic abnormality (including *FLT3*) identified at screening and include three categories of risk: favourable, intermediate and adverse (8). Per the ELN risk stratification, patients with *FLT3-ITD*+ AML (in the absence of adverse risk genetic lesions) are classified as having intermediate risk (8).

Current treatment options

All of the guidelines listed above recommend early incorporation of FLT3 inhibitors into the therapeutic regimen (6). The current approach is to combine them with anthracyclines and cytarabine in an attempt to increase the cytotoxic effect against leukaemic cells and reverse the poor prognosis (8) for newly diagnosed *FLT3*+ AML patients that are fit for intensive chemotherapy (6).

The 2022 ELN guidelines and the 2020 ESMO guidelines recommend midostaurin with standard cytarabine and an anthracycline as induction therapy, midostaurin with intermediate-dose cytarabine and/or HSCT as consolidation therapy and midostaurin alone as maintenance therapy (Table 3) (8, 44). The 2022 ELN guidelines indicate that either idarubicin or daunorubicin can be used with cytarabine in the induction phase whereas the ESMO guidelines indicate only daunorubicin should be used. The ELN guidelines also recommend a higher dose cytarabine regimen can be used in the second induction cycle (8). Both the ELN and ESMO guidelines recommend that suitable patients should undergo HSCT in the consolidation phase if feasible (8, 44).

The NHS Pan-London guidelines recommend a similar midostaurin regimen as the ELN guidelines in this indication but with high-dose rather than intermediate-dose cytarabine in the consolidation phase and with daunorubicin recommended as the anthracycline of choice in the induction phase (2). The NHS Pan-London guidelines

specify that midostaurin is recommended to be continued as single agent maintenance therapy for up to 48 weeks (2). These guidelines also highlight that most intermediate-risk patients (the ELN guidelines categorise patients with *FLT3-ITD+* AML as having intermediate risk) with AML receiving chemotherapy with curative intent should be referred to explore transplant options. They further specify that if patients are to proceed to receive HSCT, the procedure should be undertaken as soon as a complete remission (CR) is achieved (2).

Table 3. Recommended treatments in newly diagnosed patients with *FLT3+* AML that are fit for intensive chemotherapy

	UK Guidelines	European Guidelines	
	NHS	ELN	ESMO
Induction	Midostaurin + daunorubicin + cytarabine	Midostaurin + daunorubicin OR idarubicin + cytarabine Re-induction: as above or higher dose of cytarabine + midostaurin	Midostaurin + daunorubicin + cytarabine
Consolidation	Midostaurin + HiDAC and/or HSCT[a]	Midostaurin + IDAC and/or HSCT[b]	Midostaurin + IDAC and/or HSCT[c]
Maintenance	Midostaurin	Midostaurin	Midostaurin

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplant; AML, acute myeloid leukaemia; BMJ, British Medical Journal; ELN, European LeukemiaNet; ESMO, European Society for Medical Oncology; *FLT3+*, FMS-like tyrosine kinase 3 positive; HiDAC, high-dose cytarabine; IDAC, intermediate-dose cytarabine; NHS, National Health Service.
References: RM Partners, 2020 (2); ELN, 2022 (8); ESMO, 2020 (44).
Notes: a. These guidelines state 'with regards to those with intermediate-risk AML, this is a very heterogeneous group. The AML17 'high-risk' score can help to indicate those who may benefit from HSCT within this cohort. The majority of transplant physicians will consider transplant consolidation in this group of individuals, although the supporting data are mixed. Decisions regarding HSCT should be made on an individualised, case-by-case basis'. b. Use of HSCT is dependent on disease risk category (intermediate and adverse) and probability of relapse c. Patients in CR with ELN intermediate- or adverse-risk AML should undergo HSCT, if feasible.

Sorafenib has recently been recommended in a recent NHS clinical commissioning policy (published November 2023) as a maintenance treatment option for adults with FLT3-ITD AML post HSCT (63). The company do not consider sorafenib to be an appropriate comparator in this submission as it is neither licenced by the EMA or MHRA (64) nor assessed or recommended by NICE as clinically effective or cost-effective in this indication. Furthermore, sorafenib is not included in the list of comparators in the final scope for this appraisal. On this basis, sorafenib has not been included as a comparator in this submission.

B.1.3.5 Unmet need

Despite current available treatments, the unmet medical need for newly diagnosed *FLT3-ITD*+ AML remains high, since these patients have poor prognosis, suboptimal outcomes and remain at high risk of relapse, even after HSCT (10, 34, 65, 66). It is well established that the presence of a *FLT3-ITD* mutation confers a poor prognosis, with relapse being the principal cause of treatment failure for the majority of these patients. When treated with standard chemotherapy alone, *FLT3-ITD*+ AML is associated with a higher rate of relapse (67), with most relapses occurring within the first 2 years of follow-up. Furthermore, approximately 75% of patients with *FLT3-ITD*+ AML at diagnosis continue to have a detectable ITD mutation at relapse, suggesting that *FLT3-ITD* may function as a driver mutation responsible for disease progression (16, 68).

Significant improvements in survival outcomes of patients with *FLT3-ITD*+ AML have been reported with allogeneic HSCT compared with chemotherapy or autologous HSCT. However, relapse following HSCT remains high in these patients compared with those without *FLT3-ITD* mutations, with a higher 2-year relapse incidence (30% vs. 16%; p = 0.006) and lower leukaemia-free survival (58% vs. 71%; p = 0.04) (43, 69).

FLT3 inhibitors are now standard of care for patients with the *FLT3* mutations (midostaurin, gilteritinib). In the newly diagnosed AML setting, midostaurin, is the only drug that has been approved so far in the UK. Despite the recent progress in management of these *FLT3* mutated patients, the prognosis remains poor, mainly due to high risk of relapse within the first 2 years of follow-up.

Midostaurin is the only FLT3 inhibitor currently recommended in the first line treatment of *FLT3* mutation positive AML patients in the UK (see B.1.3.4). It is a first-generation, type I FLT3 inhibitor and targets both the *ITD* and *TKD* mutations (16, 70). However, type I inhibitors may lead to AEs due to their superfluous targeting of *TKD* in *FLT3-ITD*+ patients, further impacting patients' HRQoL (see B.1.3.3) (21). The RATIFY study found that patients in the midostaurin arm experienced significant improvement in overall survival. However, the reduction in risk of death provided by midostaurin was 35% in *FLT3-TKD*+ patients and only 20% in *FLT3-ITD*+ patients (who represented

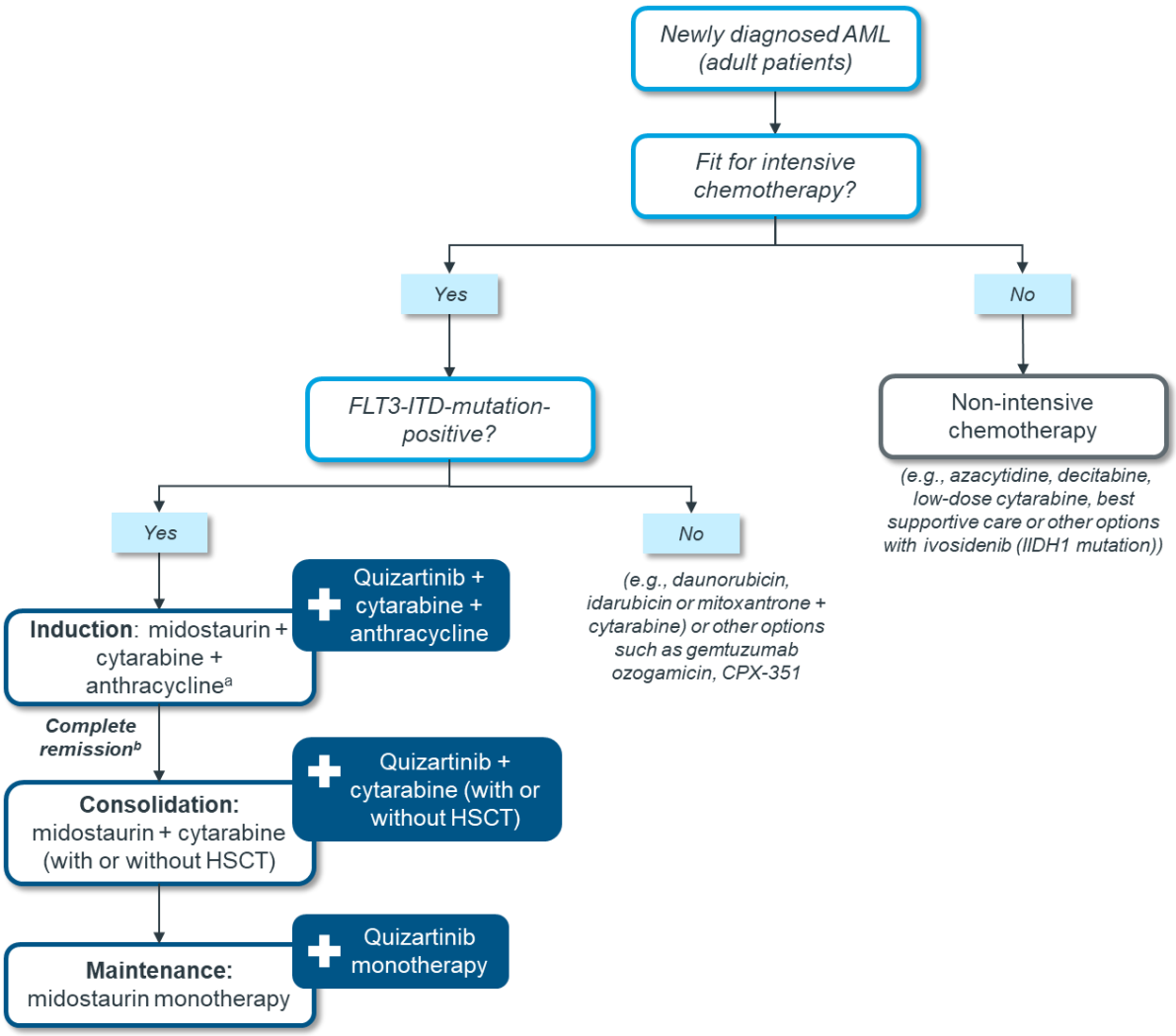
23% and 77% of the whole study population) (10). Additionally, the rate of cumulative incidence of relapse (CIR) with midostaurin was reported to be approximately 40% at 2 years of follow-up (10). Midostaurin is also associated with high treatment discontinuation rates due to factors such as adverse events (AEs) like nausea and vomiting (10). The need for twice-daily administration and the unpleasant smell of the midostaurin pill could also negatively impact the patient experience and adherence (71, 72). In addition, the effectiveness of midostaurin as monotherapy during the maintenance phase after achieving CR or after HSCT remains uncertain. Treatment guidelines do not recommend the use of midostaurin in maintenance phase following consolidation with HSCT and midostaurin is not indicated/reimbursed for post-HSCT maintenance treatment so different agents, such as sorafenib, may be used off-licence. However, medical experts have indicated that a consistent treatment that enables deep and long-lasting remission throughout induction, consolidation and maintenance would be preferable.

New treatment options for the first-line setting are therefore urgently needed for newly diagnosed *FLT3-ITD*+ AML patients.

B.1.3.6 Proposed positioning of quizartinib

Quizartinib is a highly selective and potent second-generation type II FLT3 inhibitor, targeting *FLT3-ITD* (21). It is expected to fit into the existing care pathway, in accordance with its marketing authorisation, as a first-line (1L) treatment for newly diagnosed adult patients with *FLT3-ITD*+ AML who are eligible for intensive chemotherapy. Quizartinib is expected to be administered in combination with standard chemotherapy for induction (cytarabine and anthracycline) and consolidation phases (high dose cytarabine) with or without HSCT and as monotherapy in the maintenance phase. It is proposed as an alternative treatment option to midostaurin in the current established clinical management (ECM) for untreated *FLT3-ITD*+ AML patients. The proposed positioning of quizartinib is presented in Figure 3.

Figure 3. Proposed positioning of quizartinib within current treatment pathway



Abbreviations: AML, acute myeloid leukaemia; *FLT3*, FMS-like tyrosine kinase 3; HSCT, haematopoietic stem cell transplant; *ITD*, internal tandem duplication.
References: RM Partners, 2020 (2); ELN, 2022 (8).
Notes: a. In the NHS Pan London guidelines daunorubicin is recommended whereas in the ELN guidelines either daunorubicin or idarubicin are recommended b. complete remission or complete remission with incomplete haematologic recovery.

B.1.4 Equality considerations

No equality issues were identified in relation to quizartinib.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was performed to identify and summarise the available evidence regarding the clinical efficacy and safety outcomes of current first-line treatment options in adults with newly diagnosed AML that is *FLT3-ITD*+, the population of interest was based on the NICE scope.

Extensive literature searches were undertaken in electronic databases (MEDLINE, Embase, the Cochrane Central Register of Controlled Trials [CENTRAL] and the Cochrane Database of Systematic Reviews [CDSR]), as well as conference proceedings, trial registration websites and the International Network of Agencies for Health Technology Assessment (INAHTA) database from inception to 09 May 2023. A total of 18 publications describing 11 clinical trials meeting the inclusion criteria were identified.

Appendix D provides full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one randomised controlled trial (RCT), QuANTUM-First (AC220-A-U302, NCT02668653), that evaluated the efficacy and safety of quizartinib and placebo in combination with standard induction and consolidation chemotherapy, followed by quizartinib or placebo as single-agent maintenance therapy, in adult patients with newly diagnosed *FLT3-ITD*+ AML who were fit for intensive chemotherapy.

The results of QuANTUM-First have been published by Erba et al. 2023 (21). Additional details of this trial were sourced from the Clinical Study Report (CSR) of QuANTUM-First (73), the clinical study protocol (13), the statistical analysis plan (74) and the study report for quality of life analysis (75).

An overview of this pivotal study is provided in Table 4.

Table 4. Clinical effectiveness evidence: QuANTUM-First

Study	QuANTUM-First (NCT02668653)
Study design	Phase 3, randomised, double-blind, parallel-group, placebo-controlled trial.
Population	Adults (18–75 years) newly diagnosed with *FLT3-ITD*+ AML.
Intervention(s)[a]	Induction phase (up to two 28-day cycles): • Cytarabine 100 mg/m^2/day (200 mg/m^2/day also allowed if this is the institutional or local standard) • Anthracycline (daunorubicin 60 mg/m^2/day or idarubicin 12 mg/m^2/day) • Quizartinib 35.4 mg once a day. Consolidation phase (up to four 28-day cycles): There were three options for treatment: 1) consolidation chemotherapy followed by quizartinib for 14 days, 2) HSCT or 3) consolidation chemotherapy followed by quizartinib for 14 days followed by HSCT. Doses of these therapies were as follows: • Cytarabine 3.0 g/m^2 or 1.5 g/m^2 (according to patients age) every 12 hours for a total of six doses • Quizartinib 35.4 mg once a day for 14 days. Maintenance phase (up to 36 28-day cycles)[b]: • Quizartinib 26.5 mg for 15 days and then 53 mg once a day. **The treatment regimens and required dose adjustments are described in detail in Table 5.**
Comparator(s)	The treatments received by patients in the control arm were identical to those in the intervention arm except that patient in the control arm received placebo in place of quizartinib.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem[c,d]	• **OS** • EFS • **RFS** • **AEs** • **HRQoL.**
All other reported outcomes[c]	Secondary efficacy endpoints: • **CRc rate after induction** • CR rate after induction • Percentage of subjects achieving CR and CRc with *FLT3-ITD* MRD negativity following induction therapy. Exploratory efficacy endpoints: • RFS in subjects who enter the maintenance phase

Study	QuANTUM-First (NCT02668653)
	• Duration of CR • CR rate at the end of the first induction cycle • CRc rate at the end of the first induction cycle • CRh rate after induction • MLFS rate after induction • **Transplantation rate** • Health care resource utilisation • Pharmacokinetic, pharmacodynamic and biomarker endpoints. Post-hoc analysis • **Cumulative incidence of relapse (CIR)**

Abbreviations: AE, adverse event; HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; CR, complete remission; CRc, complete composite remission; CRh, complete remission with partial hematologic recovery; *FLT3-ITD*, FMS-like tyrosine kinase 3-internal tandem duplication; *FLT3-ITD+*, FMS-like tyrosine kinase 3-internal tandem duplication positive; EFS, event-free survival; HRQoL, health related quality of life; MLFS, morphologic leukaemia-free state; MRD, minimal or measurable residual disease; OS, overall survival; RFS, relapse-free survival.
References: Erba et al. 2023 (21)
Notes: a. Base drug values rather than salt values (which are used in the Erba et al. publication) have been used in line with the quizartinib summary of product characteristics. 17.7 mg, 26.5 mg, 35.4 mg and 53 mg of quizartinib base drug are equivalent to 20 mg, 30 mg, 40 mg and 60 mg of quizartinib dihydrochloride respectively.
b. The protocol also permitted HSCT within the first three months of the maintenance phase provided the following conditions were met: 1. When the subject started the consolidation phase, the plan was for the subject to undergo HSCT as part of consolidation therapy; 2. A donor was not able to be found during the consolidation phase but became available after the start of the maintenance phase; 3. The investigator discussed the case with the medical monitor; 4. Confirmed <5% of blasts were present based on the most recent bone marrow aspirate, based on the local laboratory results; 5. The transplant is performed within 3 months after Day 1 of maintenance therapy.
c outcomes in bold are incorporated into the economic model.
d. these outcomes are consistent with the final NICE scope

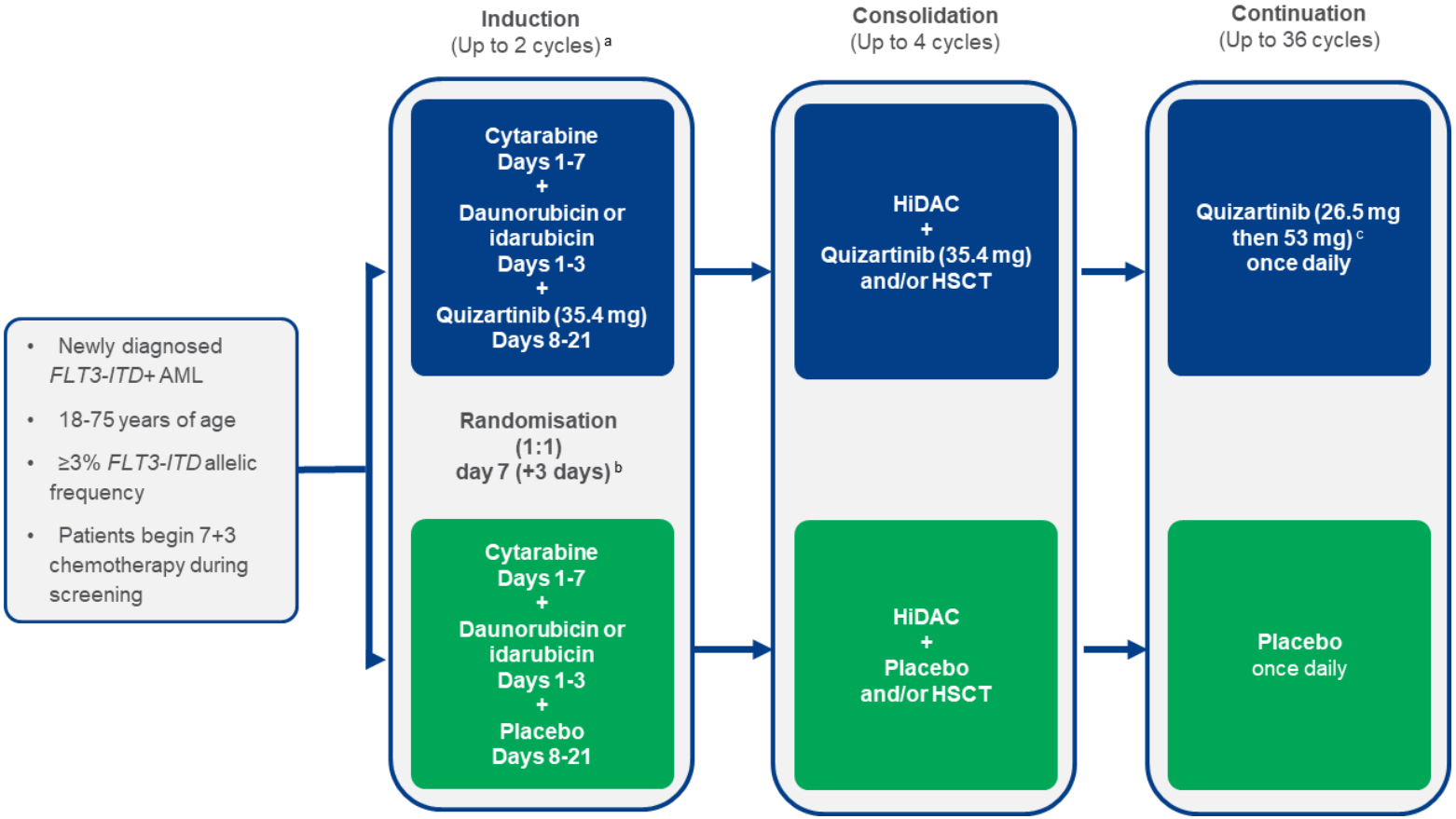
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

QuANTUM-First was an international, multi-centre, phase 3, randomised, double-blind trial, comparing the efficacy and safety of quizartinib vs. placebo (administered with standard induction and consolidation chemotherapy, then administered as maintenance therapy for up to 36 cycles of 28-days) (21).

An overview of the clinical trial design from screening through the treatment period is presented in Figure 4. The subsequent long-term follow-up phase began upon completion of 36 cycles of the study drug (quizartinib or placebo) in the maintenance phase, or permanent discontinuation of the study drug in any phase (21). The total duration of subject participation was to be until death, withdrawal of consent, loss to follow-up or study closure, whichever occurred first (21). The data cut-off date used for the analyses was 13 August 2021 and no other prespecified analyses are planned.

A summary of the QuANTUM-First study methodology is provided in Table 5.

Figure 4. Study design of the QuANTUM-First



Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; *FLT3-ITD*, FMS-like tyrosine kinase 3-internal tandem duplication; HiDAC, high-dose cytarabine.
References: Erba et al. 2023 (76)
Notes: a. During Cycle 2 of the induction phase, investigators may have chosen to administer the "7 + 3" or the "5 + 2" chemotherapy regimen, and study drug would therefore have started on Day 8 or Day 6, respectively. b. Randomisation could be delayed to days 8 to 10 to address clinical concerns (e.g. electrolyte abnormalities, QT prolongation). c. The dose of study drug on Cycle 1 Days 1 to 15 was to be 26.5 mg orally once daily. On Cycle 1 Day 16, the dose was to be increased to 53 mg/day if the average QTcF of the triplicate ECG was ≤450 ms on Cycle 1 Day 15. Once the dose was increased to 53 mg/day, the subject was allowed to continue this dose as long as dose reduction was not needed.

Table 5. Summary of QuANTUM-First clinical trial methodology

Study	QuANTUM-First (NCT02668653)
Trial design	QuANTUM-First is a phase 3, randomised, double-blind, placebo-controlled study comparing the efficacy and safety of quizartinib vs. placebo (administered with standard induction and consolidation chemotherapy, then administered as maintenance therapy for up to 36 cycles) in subjects with ND *FLT3-ITD*+ AML. Subjects were randomised into one of two treatment arms (quizartinib or placebo) in a 1:1 ratio. Randomisation was stratified based on: • Region (North America, Europe and Asia/Other Regions) • Age (<60 years old, ≥60 years old) • WBC count at the time of diagnosis of AML (<40×10^9/L, ≥40×10^9/L).
Eligibility criteria for participants	<u>Inclusion criteria for randomisation:</u> • Must have been competent and able to comprehend, sign and date an EC - or IRB - approved ICF before performance of any study-specific procedures or tests • ≥18 years or the minimum legal adult age (whichever was greater) and ≤75 years (at screening) • ND, morphologically documented primary AML or AML secondary to MDS or an MPN, based on the WHO 2008 classification (at screening) • ECOG PS 0-2, at the time the subject signed his/her first ICF • Presence of *FLT3-ITD* activating mutation in bone marrow (allelic ratio of ≥3% *FLT3-ITD*/total *FLT3*) • Subject was receiving the standard '7+3' induction chemotherapy regimen specified in the protocol • Adequate renal function: creatinine clearance >50 mL/min, as calculated with the modified Cockcroft Gault equation • Adequate hepatic function: TBL ≤1.5 × ULN unless the subject had documented Gilbert's syndrome or the increase was related to increased unconjugated (indirect) bilirubin due to haemolysis; serum alkaline phosphatase, aspartate transaminase and alanine transaminase ≤2.5 × ULN • Serum electrolytes within institution's normal limits (if outside of the institution's normal range, subject was eligible if electrolytes were corrected) • If a woman of childbearing potential, the woman needed to have a negative serum pregnancy test upon entry into the study and to be willing to use highly effective birth control upon enrolment, during the treatment period and for six months following the last dose of investigational drug or cytarabine, whichever was later. A woman was considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy)

Study	QuANTUM-First (NCT02668653)
	• If male, patients needed to be surgically sterile or willing to use highly effective birth control upon enrolment, during the treatment period and for 6 months following the last dose of investigational drug or cytarabine, whichever was later. Inclusion criteria for the consolidation phase: • Achieved CR or CRi, based on local laboratory results, at the end of the induction phase • Able to begin the consolidation phase within 60 days of Day 1 of the last induction cycle. Inclusion criteria for the maintenance phase: • Subject did not have active acute or ≥ grade 3 GVHD • Subject had not initiated therapy for active GVHD (prophylaxis is allowed) within 21 days • Confirmed <5% of blasts based on the most recent bone marrow aspirate, based on the local laboratory results, performed within 28 days prior to Cycle 1 Day 1 of maintenance therapy • Absolute neutrophil count >500/mm^3 and platelet count >50,000/mm^3 without platelet transfusion support within 24 hours prior to Cycle 1 Day 1 of maintenance therapy • Subject was able to begin maintenance phase within 60 days of Day 1 of the last consolidation cycle received or within 180 days after HSCT (i.e. stable after transplant). Exclusion criteria • Diagnosis of APL, French American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12) or BCR ABL positive leukaemia (i.e. chronic myelogenous leukaemia in blast crisis); subjects who undergo diagnostic workup for APL and treatment with ATRA, but who were found not to have APL, are eligible (treatment with ATRA must be discontinued before starting induction chemotherapy) • Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms • Prior treatment for AML, except for the following allowances: leukapheresis, treatment for hyperleukocytosis with hydroxyurea, cranial radiotherapy for CNS leukostasis, prophylactic intrathecal chemotherapy, growth factor/cytokine support • Prior treatment with quizartinib or other *FLT3-ITD* inhibitors • Prior treatment with any investigational drug or device within 30 days prior to randomisation (within two weeks for investigational or approved immunotherapy) or were currently participating in other investigational procedures

Study	QuANTUM-First (NCT02668653)
	• History of known CNS leukaemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture was recommended for subjects with symptoms of CNS leukaemia to rule out extramedullary CNS involvement • History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease or other solid tumours curatively treated with no evidence of disease for at least two years • Uncontrolled or significant cardiovascular disease, including any of the following: o Bradycardia of less than 50 beats per minute, unless the subject has a pacemaker o QTcF interval >450 ms o Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome) o Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg o History of clinically relevant ventricular arrhythmias (e.g. ventricular tachycardia, ventricular fibrillation or Torsade de Pointes) o History of second (Mobitz II) or third-degree heart block (subjects with pacemakers were eligible if they had no history of fainting or clinically relevant arrhythmias while using the pacemaker) o History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to screening o History of NYHA class 3 or 4 heart failure o LVEF ≤45% or less than the institutional lower limit of normal per MUGA or echocardiogram done within 30 days prior to randomisation o Complete left bundle branch block • Active acute or chronic systemic fungal, bacterial or viral infection not well controlled by antifungal, antibacterial or antiviral therapy • Known active clinically relevant liver disease (e.g. active hepatitis B or active hepatitis C) • Known history of HIV. Subjects should have been tested for HIV prior to randomisation if required by local regulations or EC. • History of hypersensitivity to any excipients in the quizartinib or placebo tablets • Females who were pregnant or breastfeeding • Otherwise considered inappropriate for the study by the investigator.
Settings and locations where the data were collected	This is a global study and subjects were enrolled and treated at 193 study sites in the following 26 countries: Spain, Italy, Republic of Korea, Japan, China, US, France, Brazil, Germany, Russian Federation, Taiwan, Hungary, Czech Republic, Romania, Israel, Canada, Serbia, Poland, Portugal, Australia, Belgium, Bulgaria, Croatia, Ukraine, Singapore and the United Kingdom.

Study	QuANTUM-First (NCT02668653)
	In the induction phase, all subjects were to have commenced therapy as hospital inpatients and oral study drug was to be administered under nursing supervision. Subjects discharged from the hospital with quizartinib or placebo during the consolidation and maintenance phases were to return for each phase, and compliance was to be assessed by the returned tablet count.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered): **- Intervention (ITT: n=268)** **- Comparator (ITT: n=271)**	The study consisted of four consecutive treatment phases: induction, consolidation, maintenance and long-term follow-up. In the first three phases each cycle was 28 days in duration. However, additional time was allowed for recovery of blood counts or other reasons, if needed, in the induction or consolidation phases. The treatment regimens for each arm of the study differ only in the administration of quizartinib in the intervention arm vs. placebo in the control arm. The dosing schedule used in each treatment phases are described below. **Induction phase** Subjects were permitted to receive up to two cycles of induction chemotherapy. During Cycle 1 subjects received the following treatment schedule: • Cytarabine 100 mg/m^2/day (200 mg/m^2/day was allowed if this was the institutional or local standard) by continuous IV infusion on Days 1–7 • One of the following anthracycline regimens (investigator's choice): o Daunorubicin 60 mg/m^2/day IV infusion on Days 1–3 o Idarubicin 12 mg/m^2/day IV infusion on Days 1–3 • **Quizartinib** 35.4 mg (17.7 mg/day for subjects concomitantly receiving a strong CYP3A4 inhibitor) **or placebo** (according to randomisation) administered orally once daily on Days 8–21 (randomisation 1:1 occurred on Day 7). At the investigator's discretion, to allow for blood counts to recover or other reasons, a second induction cycle was permitted to start up to 60 days after Day 1 of the first induction cycle. Subjects with ≥ 5% blasts after Cycle 1 were allowed to receive a second cycle of induction, if appropriate. During Cycle 2 patients received the following treatment schedule: • One of the following chemotherapy regimens: o '7+3': 7 days of continuous IV infusion of standard dose cytarabine plus 3 days of anthracycline (same anthracycline used in Cycle 1) o '5+2': 5 days of continuous IV infusion of standard dose cytarabine plus 2 days of anthracycline (same anthracycline used in Cycle 1) • **Quizartinib** 35.4 mg (17.7 mg/day for subjects concomitantly receiving a strong CYP3A4 inhibitor) **or placebo** (according to randomisation) administered orally once daily for 14 days on Cycle 2 Day 8 or Cycle 2 Day 6, depending on the chemotherapy regimen selected (initiated at the end of the cytarabine infusion).

Study	QuANTUM-First (NCT02668653)
	Consolidation phase Patients who met the consolidation phase inclusion criteria were allowed to proceed to this phase. Subjects were permitted to receive up to four cycles of consolidation therapy, if tolerated. Three therapy options were possible in this phase: 1) Consolidation chemotherapy followed by **quizartinib or placebo** (according to randomisation) for 14 days 2) HSCT 3) Consolidation chemotherapy followed by **quizartinib or placebo** (according to randomisation) for 14 days followed by HSCT. Details of the treatments in the above therapy options are described below: • Consolidation chemotherapy: Cytarabine was to be given on Days 1, 3 and 5. The cytarabine regimen was as follows: o For subjects <60 years: cytarabine 3.0 g/m^2 by IV infusion, every 12 hours for a total of 6 doses o For subjects ≥60 years: cytarabine 1.5 g/m^2 by IV infusion, every 12 hours for a total of 6 doses • Quizartinib 35.4 mg (17.7 mg/day for subjects concomitantly receiving a strong CYP3A4 inhibitor) or placebo (according to randomisation) was to be administered orally once daily for 14 days starting on Day 6 • HSCT: Patients were permitted to undergo HSCT if they had achieved and were still in CR or CRi. Study drug was to be discontinued at least 7 days before the start of a conditioning regimen. **Maintenance phase** After induction and consolidation therapy and upon blood count recovery (ANC >500/mm^3 and platelet count >50,000/mm^3 without a platelet transfusion within 24 hours of drawing blood samples), subjects who met the maintenance phase inclusion criteria could begin the third phase of the RCT. For subjects who underwent HSCT, maintenance therapy was to begin any time between 30 and 180 days after the transplant. Study drug was to be administered orally once daily starting on Day 1, with no breaks in dosing between cycles. If study drug was interrupted, missed doses were not to be made up. In addition, according to the investigator's discretion, subjects who achieved CR or CRi following induction, but were unable to receive consolidation therapy, were permitted to enter the maintenance phase if they met the maintenance phase inclusion criteria. During this phase patients received the following treatment schedule: • **Quizartinib** 26.5 mg/day (17.7 mg/day for subjects concomitantly receiving a strong CYP3A4 inhibitor) **or placebo** (according to randomisation) administered orally once daily on Cycle 1 Days 1–15 • **Quizartinib** 53 mg (26.5 mg/day for subjects concomitantly receiving a strong CYP3A4 inhibitor) **or placebo** (according to randomisation) administered orally once daily from Cycle 1 Day 16.

Study	QuANTUM-First (NCT02668653)
	The quizartinib dose only increased on Cycle 1 Day 16 if the average QTcF of the triplicate ECG was ≤450 ms on Cycle 1 Day 15. Patients were allowed to continue taking this increased dose as long as dose reduction was not needed. If it was not possible to increase the dose on Cycle 1 Day 16, the dose could have been increased on Cycle 2 Day 2 if the average QTcF of the triplicate ECG was ≤450 ms on Cycle 2 Day 1. HSCT was also possible within the first three months of this phase provided certain criteria defined in the protocol were met. Maintenance therapy was to continue for up to 36 cycles until relapse, start of non-protocol-specified AML treatment, death, unacceptable toxicity, study closure or completion of study drug (36 cycles), whichever occurred first. **Long-term Follow-up phase** The long-term follow-up phase began upon completion of 36 cycles of study drug (quizartinib or placebo) in the maintenance phase or upon permanent discontinuation of study drug in any phase.
Permitted and disallowed concomitant medication	Permitted concomitant medication • Strong CYP3A4 inhibitors were recommended to be avoided whenever possible, but if they were necessary for subject care, they were allowed with a corresponding dose reduction of the study drug • No restrictions for moderate or weak CYP3A4 inhibitors were applied • Co-administration of quizartinib with drugs that were substrates of P-glycoprotein was permitted with due caution. Disallowed concomitant medication • Patients were not allowed to receive concomitant chemotherapy, immunotherapy, radiotherapy, transplant or any ancillary therapy for AML that was not specified in the protocol or that was considered to be investigational while on the study drug • Medications associated with QT/QTc prolongation were prohibited. Exceptions were permitted for therapies required for the prevention or treatment of infections or if the investigator believed that beginning therapy with a potentially QTc-prolonging medication was vital to an individual subject's care • Strong or moderate CYP3A4 inducers were prohibited.
Primary outcomes (including scoring methods and timings of assessments)	OS measured from the date of randomisation to the date of death from any cause.

Study	QuANTUM-First (NCT02668653)
Other outcomes used in the economic model/specified in the scope	• EFS • CRc rate • RFS • Transplantation rate • QoL
Pre-planned subgroups	OS, EFS and safety endpoints were also analysed for the following subgroups: • Age: <60 years, ≥60 years to <65 years, ≥65 years[a] • Sex: Male, Female[a] • Race: White, Black or African American, Asian, other defined in eCRF[a] • Choice of anthracycline: daunorubicin, idarubicin[a] • Region: North America, Europe, Asia/other regions[b] • WBC count at the time of diagnosis of AML: <40 × 10^9/L, ≥40 × 10^9/L[b] • AML cytogenetic risk score: favourable, intermediate, unfavourable, unknown[b] • Baseline ECOG PS: 0, 1, 2[b] • *FLT3-ITD* VAF (using central testing) at randomisation: <3%, ≥3% to ≤25%, >25% to ≤50%, >50%[b] • NPM-1 mutational status: yes, no[b] • Concomitant use of strong CYP3A4 inhibitor: yes, no[c] • Concomitant use of QT-prolonging medications in AZCERT classification "known risk": yes, no[c].

Abbreviations: HSCT, Allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; APL, acute promyelocytic leukaemia; ATRA, all-trans retinoic acid; AZCERT, The Arizona Center for Education and Research on Therapeutics; CIs, confidence interval; CNS, central nervous system; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; CYP3A4, cytochrome P450 3A4; EC, ethics committee; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; eCRF, electronic case report form; EFS, event-free survival; *FLT3-ITD*, FMS-like tyrosine kinase 3 - internal tandem duplication; *FLT3-ITD+*, FMS-like tyrosine kinase 3 - internal tandem duplication positive; GVHD, graft-vs.-host disease; HIV, human immunodeficiency virus; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICF, informed consent form; IRB, Institutional Review Board; ITT, intent-to-treat; IV, intravenous; LVEF, Left ventricular ejection fraction; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MUGA, multigated acquisition scan; ND, newly diagnosed; NPM-1, nucleophosmin 1; NYHA, New York Heart Classification; OS, overall survival; QoL, quality of life; QT, interval between the start of the Q wave and the end of the T wave; QTc, corrected QT interval; QTcF, QT interval corrected with Fridericia's formula; RCT, randomised controlled trial; RFS, relapse-free survival; TBL, total bilirubin; ULN, upper limit of normal; US, United States; VAF, variant allele frequency; WBC, white blood cell; WHO, World Health Organization.
References: Erba et al. 2023 (21); Erba et al. 2023 (76)
Notes: a. These subgroups were analysed for EFS, OS and safety endpoints. b. These subgroups were analysed for EFS and OS endpoints only. c. These subgroups were analysed for a safety endpoint (ECG) only

Definitions of outcomes assessed in QuANTUM-first are described in Table 6.

Table 6. Outcome definitions and response criteria used in QuANTUM-First

Endpoint	Definition
Outcome definitions	
OS	The time from the date of randomisation to the date of death from any cause.
EFS	The time from randomisation to either refractory disease (ITF), relapse after CR or CRi, or death from any cause, whichever occurred first. The definition of refractory disease used in the primary, sensitivity and supplementary EFS analyses varied as outlined in the response criteria section of this table.
CRc rates	The percentage of subjects achieving CR or CRi after induction.
RFS	The time from randomisation, for patients who achieved CRc[b] during induction, until the date of documented relapse or death from any cause, whichever occurred first.
Duration of CR	The time from the first documented CR until documented relapse or death from any cause, whichever came first
Transplantation rate	The percentage of subjects undergoing protocol-specified HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens)
QoL	EQ-5D-5L scores of patients at each trial visit and changes in EQ-5D-5L scores over time
MRD	MRD is the presence of a small number of leukaemic cells in the bone marrow of patients with AML below the level of detection using conventional morphologic assessment.
AE	Any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
TEAE	An AE that occurred or worsened in severity after the first dose of study drug up to 30 days after the last dose of study drug. An AE collected more than 30 days after the last dose of quizartinib or placebo will not be considered a TEAE unless it was considered drug-related.
Drug-related TEAE	A TEAE assessed as related to the study drug by the investigator.
SAE	An SAE is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is an important medical event.
Response criteria	

Endpoint	Definition
Refractory disease	For the primary analysis of EFS, refractory disease (or ITF) is defined as: • CR never achieved in the induction phase within a 42-day window from the start of the last induction cycle; or • Blasts <5% if Auer-rod positive; or • Appearance of new or worsening extramedullary disease. For EFS sensitivity and supplementary analyses, refractory disease (or ITF) is defined as: • CR (sensitivity analysis) or CRc (supplementary analysis) never achieved in the induction phase within a 56-day window from the start of the last induction cycle; or • Blasts <5% if Auer-rod positive; or • Appearance of new or worsening extramedullary disease. In both cases for refractory disease, the EFS event date will be set to Day 1 at randomisation.
Relapse after CR or CRi	Relapse after CR or CRi is defined as: • ≥5% blasts in the bone marrow aspirate and/or biopsy not attributable to any other cause; or • Reappearance of leukaemic blasts in the peripheral blood; and/or • New appearance of extramedullary leukaemia; or • Presence of Auer rods
CR	>1,000 neutrophils, >100,000 platelets, <5% blasts, no EMD, no Auer rods and an absence of leukaemic blasts in the peripheral blood by morphological examination
CRi	CRi meets criteria for CR except for the platelet or neutrophil count. CRi is defined as CR with incomplete platelet recovery (>1,000 neutrophils, ≤100,000 platelets, <5% blasts) or CR with incomplete neutrophil recovery (≤1,000 neutrophils, >100,000 platelets, <5% blasts).
MRD negativity	Assessed with next-generation sequencing and based on a two cut-offs of leukaemia cells: < 1 x 10^{-4} and 0.

Abbreviations: AE, adverse event; HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; EFS, event-free survival; EMD, extramedullary disease; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EQ-5D-5L, EuroQoL-5D-5L; *FLT3-ITD*, FMS-like tyrosine kinase 3 - internal tandem duplication; ITF, induction treatment failure; MRD, minimal or measurable residual disease; OS, overall survival; QoL, quality of life; RFS, relapse-free survival; SAE, serious adverse event; TEAE, treatment emergent adverse event.
References: Erba et al. 2023 (21); Erba et al. 2023 (76)
Notes: a. An analysis was also conducted which defined RFS as the time from randomisation, for patients who achieved CR during induction, until the date of documented relapse or death from any cause, whichever occurred first.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis Sets

Four analysis sets were considered in the statistical analysis of QuANTUM-First: the intent-to-treat (ITT) analysis set, the safety analysis set, the per-protocol analysis set, and the patient-reported outcome (PRO) analysis set. The number of patients in each analysis set is summarised in Table 7.

Table 7. Analysis sets in the QuANTUM-First study

Analysis set	Quizartinib (N=268) n (%)	Placebo (N=271) n (%)	Total (N=539) n (%)
Intention-to-treat	268 (100)	271 (100)	539 (100)
Safety	265 (98.9)	268 (98.9)	533 (98.9)
Per-protocol	[redacted]	[redacted]	[redacted]
PRO	[redacted]	[redacted]	[redacted]

Abbreviations: PRO, patient-reported outcome.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21); Daiichi Sankyo, 2022 (75)

ITT analysis set

The ITT analysis set included all subjects who were randomised. All efficacy analyses were performed based on this analysis set (21).

Safety analysis set

The safety analysis set included all subjects who received at least one dose of quizartinib or placebo. Safety analyses were performed using this analysis set (21).

Per-protocol analysis set

The per-protocol population included all subjects in the ITT analysis set who had no major protocol deviations that would affect assessment of efficacy endpoints (21).

The protocol indicated that efficacy analysis based on the per-protocol set may be performed if the ITT analysis set differs from per protocol analysis set by more than 10%. This threshold was not reached and thus the efficacy analyses were not conducted using the per-protocol analysis set (73).

Patient-reported outcome (PRO) analysis set

The EuroQol-5D-5L (EQ-5D-5L) analysis set included all subjects in the ITT analysis set who completed the relevant EQ-5D-5L assessments at screening (Day 8 of the induction phase Cycle 1) (21).

B.2.4.2 Patient disposition

For detailed information on patient disposition in the trial, please see Appendix D.

B.2.4.3 Baseline characteristics

Demographic and selected baseline characteristics are summarised descriptively by treatment arm in Table 8. In general, these characteristics were consistent with the *FLT3-ITD*+ AML population and well balanced between the treatment arms.

Table 8. Demographic and disease baseline characteristics

Characteristic	Quizartinib	Placebo	Total
ITT analysis set			
	N=268	**N=271**	**N=539**
Age (years)			
Mean (SD)	53.6 (13.1)	54.3 (12.8)	54.0 (12.9)
Median	56.0	56.0	56.0
Proportion ⩾60 years, n (%)	107 (39.9)	109 (40.2)	216 (40.1)
Sex, n (%)			
Male	124 (46.3)	121 (44.6)	245 (45.5)
BMI (kg/m^2)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Race, n (%)			
Asian	80 (29.9)	78 (28.8)	158 (29.3)
Black or African American	2 (0.7)	5 (1.8)	7 (1.3)
American Indian or Alaska Native	0	1 (0.4)	1 (0.2)
Native Hawaiian/Pacific Islander	0	0	0
White	159 (59.3)	163 (60.1)	322 (59.7)
Other	27 (10.1)	24 (8.9)	51 (9.5)
Ethnicity, n (%)			
Hispanic/Latino	[redacted]	[redacted]	[redacted]

Characteristic	Quizartinib	Placebo	Total
Non-Hispanic/Non-Latino	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Region, n (%)			
North America	16 (6.0)	18 (6.6)	[redacted]
Europe	163 (60.8)	163 (60.1)	[redacted]
Asia/other regions	89 (33.2)	90 (33.2)	[redacted]
ECOG, n (%)			
0	87 (32.5)	98 (36.2)	[redacted]
1	134 (50.0)	136 (50.2)	[redacted]
2	47 (17.5)	36 (13.3)	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Time from diagnosis to randomisation (weeks)[a]			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
AML type, n (%)			
De novo AML	243 (90.7)	255 (94.1)	[redacted]
Secondary AML	25 (9.3)	16 (5.9)	[redacted]
WBC count at diagnosis of AML, n (%)			
<40 × 10^9/L	135 (50.4)	137 (50.6)	[redacted]
≥40 × 10^9/L	133 (49.6)	134 (49.4)	[redacted]
Risk status with specific cytogenetic patterns, n (%)b			
Favourable	14 (5.2)	19 (7.0)	[redacted]
Intermediate	197(73.5)	193 (71.2)	[redacted]
Unfavourable	19(7.1)	27 (10.0)	[redacted]
Unknown	38 (14.2)	31 (11.4)	[redacted]
Missing	0	1 (0.4)	[redacted]
***FLT3-ITD* VAF by central laboratory testing (*FLT3-ITD*/total *FLT3*), n (%)[c]**			
≥3% to ≤25%	94 (35.1)	98 (36.2)	[redacted]
>25% to ≤50%	143 (53.4)	138 (50.9)	[redacted]
>50%	30 (11.2)	35 (12.9)	[redacted]
AML with recurrent genetic abnormalities, n (%)			
AML with mutated *NPM1*	142 (53.0)	140 (51.7)	[redacted]
AML with mutated CEBPA[d]	61 (22.8)	65 (24.0)	[redacted]
Choice of anthracycline, n (%)			
Daunorubicin	[redacted]	[redacted]	[redacted]
Daunorubicin (C2), idarubicin (C1)	[redacted]	[redacted]	[redacted]
Idarubicin	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Prior treatment for AML			

Characteristic	Quizartinib	Placebo	Total
Leukapheresis	[redacted]	[redacted]	[redacted]
Treatment for hyperleukocytosis with hydroxyurea	[redacted]	[redacted]	[redacted]
Prophylactic intrathecal chemotherapy	[redacted]	[redacted]	[redacted]
Growth factor/cytokine support	[redacted]	[redacted]	[redacted]
Safety analysis set			
	N=265	**N=268**	**N=533**
Prior medical and surgical history, n (%)			
Subjects with prior medical/ surgical history	[redacted]	[redacted]	[redacted]
Prior medications other than AML treatment[e]			
Subjects with any prior medications	[redacted]	[redacted]	[redacted]
Antibacterials for systemic use	[redacted]	[redacted]	[redacted]
Antiemetics and antinauseants	[redacted]	[redacted]	[redacted]
Blood substitutes and perfusion solutions	[redacted]	[redacted]	[redacted]
Antigout preparations	[redacted]	[redacted]	[redacted]
Analgesics	[redacted]	[redacted]	[redacted]
Antimycotics for systemic use	[redacted]	[redacted]	[redacted]
Transfusions prior to induction and most common product, n (%)			
Blood product transfusion	[redacted]	[redacted]	[redacted]
Concomitant medications (most commonly reported [≥80% of subjects] ATC level 2 class), n (%)			
Subjects with any concomitant medications	[redacted]	[redacted]	[redacted]
Antibacterials for systemic use	[redacted]	[redacted]	[redacted]
Antimycotics for systemic use	[redacted]	[redacted]	[redacted]
Drugs for acid-related disorders	[redacted]	[redacted]	[redacted]
Analgesics	[redacted]	[redacted]	[redacted]

Characteristic	Quizartinib	Placebo	Total
Antiemetics and antinauseants	[redacted]	[redacted]	[redacted]
Blood substitutes and perfusion solutions	[redacted]	[redacted]	[redacted]
Concomitant strong CYP3A4 Inhibitors, n (%)			
Subjects with any concomitant strong CYP3A4 inhibitor	[redacted]	[redacted]	[redacted]

Abbreviations: AML, acute myeloid leukaemia; ATC, Anatomical Therapeutic Chemical; BMI, body mass index; C1, Cycle 1; C2, Cycle 2; CEBPA, CCAAT enhancer-binding protein alpha; CYP3A4, cytochrome P450 3A4; ECOG, Eastern Cooperative Oncology Group; *FLT3-ITD*, FMS-like tyrosine kinase 3-internal tandem duplication; ITT, intent-to-treat; max, maximum; MDS, myelodysplastic syndrome; min, minimum; *NPM1*, nucleophosmin 1; NR, not reported; SD, standard deviation; VAF, Variant allele frequency; WBC, white blood cell.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: N numbers are provided with respective outcomes when they differ from the N number provided in the analysis sets. a. Duration of disease is defined as (randomisation date minus disease diagnosis date + 1)/7. b. Favourable: inv(16), t(16;16), t(8;21), t(15;17); Intermediate: normal, +8, +6, -y; Unfavourable: del5q, -5, del7q, -7, complex. c. *FLT3-ITD* VAF refers to the allelic ratio of *FLT3-ITD*/Total *FLT3*. d. CEBPA mutation assessment as determined by all mutations present. e. only the most common were reported (≥40% of total patients)

B.2.4.4 Statistical information

The statistical analysis methods used in the QuANTUM-First clinical programme are described in Table 9.

Table 9. Summary of statistical analyses in the QuANTUM-First study

	QuANTUM-First study
Primary objective	To compare the effect of quizartinib vs. placebo (administered with standard induction and consolidation chemotherapy, then administered as maintenance therapy for up to 36 cycles) on the primary endpoint of OS in subjects with ND AML with *FLT3-ITD* mutations.
Primary hypothesis	Quizartinib prolongs OS in subjects with ND *FLT3-ITD*+ AML aged ≥18 and ≤75 years when administered with standard induction and consolidation chemotherapy, then administered as maintenance therapy for up to 36 cycles.
Multiple Comparisons/Multiplicity	A serial hierarchically ordered gatekeeping strategy was used to address the multiplicity issue and control for the family-wise type I error rate for primary and secondary efficacy endpoints. For a test to be considered statistically significant within the pre-defined testing hierarchy, it had to be statistically significant and all previous tests (if any) within the hierarchy must have been statistically significant at the 0.05 level (2-sided).
Statistical analysis	Primary endpoint (OS) • The null hypothesis was that the survival functions for OS in the quizartinib and placebo arms were equal • A stratified log-rank test was performed to test the treatment effect between the two treatment arms at the overall 2-sided α = 0.05 level, with the three stratification factors used at randomisation (region [North America, Europe, Asia/other regions], age [<60 years, ≥60 years] and WBC count at the time of diagnosis of AML [<40 × 10^9/L, ≥40 × 10^9/L]) • OS was calculated as: date of death – date of randomisation + 1 • OS was expressed as the number of months from randomisation to death. The number of months was calculated by dividing the number of days by 30.4375 • A stratified Cox PH model, with the three stratification factors used at randomisation, was used to estimate HR with 95% CI • KM methods were used to calculate the median OS (estimated for each treatment group from the 50th percentile of the corresponding KM estimates) and the corresponding 95% CI of each treatment group was calculated using the Brookmeyer and Crowley method

	QuANTUM-First study
	• OS rates at fixed timepoints were derived from the KM estimate and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survival function • Sensitivity and supplementary analyses of OS were conducted to examine the robustness of the OS. The same analysis methods and testing used for the primary OS analysis were applied to the following analyses: 1. OS analysis unstratified and 2. OS censored at the start of the conditioning regimen for HSCT conducted at any time during the study. <u>Key secondary endpoint (EFS)</u> • The null hypothesis was that the survival functions for EFS in the quizartinib and placebo treatment arms were equal • EFS was analysed using the same stratified log-rank test, KM methods and stratified Cox PH model as OS • EFS was calculated as: date of event – date of randomisation + 1 • EFS was expressed as the number of months from randomisation to EFS event. The number of months was calculated by dividing the number of days by 30.4375 • EFS rates at fixed timepoints were derived from the KM estimate and corresponding CIs were derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survival function • Sensitivity and supplementary analyses of EFS were conducted to examine the robustness of the EFS. The same analysis methods and testing used for the primary EFS analysis were applied. These analyses used alternative definitions of ITF based on CR or CRc evaluation in the induction phase (without the 42-day window). <u>Other secondary efficacy endpoints</u> • The Clopper-Pearson method was used to calculate the 2-sided 95% CIs of CR rates, CRc rates and rates of subjects achieving CR and CRc with MRD negativity at the end of induction (based on IRC assessment) • The Cochran-Mantel-Haenszel test stratified by the stratification factors used in randomisation was used to compare the CR and CRc rates at a 2-sided significance level of 0.05. <u>Exploratory efficacy outcomes</u> • RFS was calculated by treatment group using the KM method for subjects achieving CRc[a]. The KM estimate and the 2-sided 95% CIs (calculated using the Brookmeyer and Crowley method) were used to calculate the median RFS for the subjects who achieved CR in the induction phase. The RFS HR with 95% CI was estimated using unstratified Cox regression. Subjects who were alive without relapse or who were lost to follow-up at the time of the analysis were considered censored at the date of their last

	QuANTUM-First study
	response/relapse assessment. Subjects without a documented response of CR were excluded from the analysis • The duration of CR, CRc and CRi were analysed similarly to RFS • The rates of CR or CRc at the end of the first induction cycle, the rate of HSCT and the rate of CRh and MLFS after induction were summarised by treatment arm with a point estimate and associated 2-sided 95% CI constructed using Clopper-Pearson's method • The analyses of PRO endpoints were performed on the PRO analysis set. The EQ-5D-5L scores as well as changes from the PRO baseline (induction phase Cycle 1 Day 8) were analysed as continuous dependent variables at each assessment visit. Presented statistics included mean (SD) and 95% CIs around the mean, median (interquartile range), minimum and maximum values. The changes from PRO baseline categorised as improved, stable and worsened were also analysed at each assessment visit. Presented statistics included frequency and percentage of each category. The changes in the QoL scores from PRO baseline were examined via a series of MMRMs that summarised the individual change in QoL scores over time and systematic differences in changes between groups. <u>Safety outcomes</u> • Safety and tolerability were assessed by incidence, severity and changes from baseline for all relevant parameters including TEAEs, clinical laboratory tests, vital signs and ECGs. AESIs were also assessed by incidence and severity.
Sample size, power calculation	A piecewise exponential model was used to account for a plateau effect predicted due to observations in the RATIFY study (a study designed to determine the effect of the addition of midostaurin to standard chemotherapy in patients with AML and a *FLT3* mutation) of a plateau effect in OS that occurred after 30 months of treatment in the control group (10). Through simulations, factors such as sample size, timing of analysis and power were determined. In the RATIFY study survival rates of approximately 42% at 30 months and 38% at 60 months in the *FLT3-ITD* group were observed in the control group. This translated into a hazard rate of 0.029 in the first 30 months and 0.003 afterwards in the control arm. Based on this information, the simulation assumed a hazard rate of 0.029 in the first 30 months (from randomisation) and 0.003 afterwards in the placebo arm and an HR of 0.7 and 1, respectively, before and after the first 30 months between the two treatment arms. This was equivalent to an assumed survival rate of 54% at 30 months and 50% at 60 months in the quizartinib arm. Simulations indicated that about 84% power and 287 events would need to be obtained to achieve a statistically significant difference in OS distribution with approximately 536 subjects by a 2-sided log-rank test at the 0.05 significance level when OS was analysed at 24 months after the last subject was randomised.

	QuANTUM-First study
	The OS analysis was to have been performed: • When the target 287 OS events were observed and a minimum of 24 months had elapsed since the last subject had been randomised • If the target 287 OS events were not achieved by 24 months since the last subject had been randomised, then the analysis was to have been performed at a maximum of 30 months after the last subject had been randomised.
Data management, patient withdrawals	Censoring rules: • OS: Subjects who were alive at the time of data cut-off date, withdrew consent or who were lost to follow-up were considered censored. Subjects without an OS event were censored at their last known date alive • EFS: Subjects with no post-baseline response assessment and no death date were censored. Subjects that had CR but no subsequent relapse or death were censored at the date of their last response assessment on or before cut-off date • RFS: Only subjects who have a response of CRc[a] were included for analysis. Subjects having no subsequent relapse or death were censored at the date of their last response assessment on or before cut-off date • Duration of CR: Subjects alive without relapse or lost to follow-up were censored at the date of their last response assessment • QoL outcomes: At the item level, missing responses were managed as per the appropriate scoring manual. For the EQ-5D-5L, missing data were not imputed or replaced for individual items or the VAS.

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, Complete remission with incomplete neutrophil or platelet recovery; ECG, electrocardiogram; EFS, event-free survival; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EQ-5D-5L, EuroQoL 5D-5L; *FLT3-ITD*, FMS-like tyrosine kinase 3 - internal tandem duplication; HR, hazard ratio; IRC, Independent Review Committee; ITF, induction treatment failure; ITT, intent-to-treat; KM, Kaplan-Meier; MLFS, morphologic leukaemia-free state; MMRM, mixed-effects model for repeated measures; MRD, minimal or measurable residual disease; ND, newly diagnosed; OS, overall survival; PH, proportional hazards; PRO, patient-reported outcome; QoL, quality of life; RFS, relapse-free survival; RFS, relapse-free survival; SD, standard deviation; TEAE, treatment-emergent adverse event; VAS, Visual analogue scale; WBC, white blood cell.
References: Erba et al. 2023 (21); Daiichi Sankyo, 2022 (73); Daiichi Sankyo, 2021 (74)
Notes: a. the same statistical methods were used to calculate RFS in the additional analysis of RFS in which it was defined as the time from randomisation, for patients who achieved CR during induction, until the date of documented relapse or death from any cause, whichever occurred first.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessment tool for parallel group RCTs suggested by NICE (77) was used to assess the quality of the QuANTUM-First RCT (Table 10). Overall, the study was deemed to have a low risk of bias.

Table 10. Quality assessment results for the QuANTUM-First study

Study question	QuANTUM-First
Was randomisation carried out appropriately?	Yes. Randomisation was stratified by age, region and WBC count at the time of diagnosis of AML.
Was the concealment of treatment allocation adequate?	Yes. Randomisation was managed through an interactive web/voice response system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Subjects were well balanced between the treatment arms for demographic and baseline characteristics, baseline general medical history and baseline AML characteristics.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. This study had a double-blind design. Neither the subjects nor any of the investigators, sponsor or CROs were aware of the treatments received.
Were there any unexpected imbalances in drop-outs between groups?	No. At the time of data cut-off the primary reasons for study discontinuation were the same for both groups: death (49.6% for the quizartinib arm and 58.3% for the placebo arm), withdrawal of consent (4.9% for the quizartinib arm and 3.3% for the placebo arm) and lost to follow-up (0.7% for the quizartinib arm and 0.4% for the placebo arm). Study drug discontinuation due to AEs was more common in the quizartinib arm than in the placebo arm (21.9% vs. 8.6% respectively). In the placebo arm, study drug discontinuation due to refractory disease and relapse were more common than in the quizartinib arm (26.1% vs. 15.5% respectively, and 24.3% and 16.6% respectively). However, such imbalances were not unexpected.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Results are described for all planned outcomes listed in the trial protocol.
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the efficacy analyses were performed using the ITT analysis set which was appropriate for this trial. Yes. Table 9 provides a summary of the censoring rules.
Did the authors of the study publication declare any conflicts of interest?	Yes. Seven of the authors are employees of DS. Several of the authors report grants and/or have been paid consulting fees including for participation on advisory boards by DS. Additionally, one author received payments for lectures, one is on a data safety

Study question	QuANTUM-First
	monitoring board/advisory board for DS and another received equipment from DS.

Abbreviations: AML, acute myeloid leukaemia; CRO, contract research organisation; DS, Daiichi Sankyo; ITT, intent-to-treat; WBC, white blood cell.
References: Erba et al. 2023 (21); Daiichi Sankyo, 2022 (73)

The included population was representative of the general population of patients with newly diagnosed *FLT3-ITD+* AML. For example, 53% of patients in the quizartinib arm and 52% of patients in the placebo arm had an *NPM1* mutation, which demonstrates a similar rate of concurrent *NPM1* mutations compared with real-world populations (78). The study also allowed the safety of quizartinib to be evaluated in a patient population with risk factors for prolongation of the QT interval, to ensure the results were reflective of the general newly diagnosed *FLT3-ITD+* AML patient population. Furthermore, there was a high enrolment of subjects from Europe (about 60%), hence, subjects were likely to be representative of patients in the UK; this was confirmed with expert clinical opinion in the UK.

B.2.6 Clinical effectiveness results of the relevant studies

Results of the following efficacy outcomes are described in this section:

- **Primary efficacy outcome**: OS
- **Secondary efficacy outcomes**: EFS and composite complete remission (CRc) rates
- **Exploratory efficacy outcomes**: relapse-free survival (RFS), duration of CR, transplantation rate and quality of life (QoL).

A summary of the efficacy endpoints results is presented in Table 11.

Table 11. Summary of efficacy data from the QuANTUM-First trial

Endpoint	Quizartinib	Placebo	p-value or HR (95% CI)[a]
Median OS, months 1-year, % 2-year, % 3-year, % 4-year, %	31.9 [redacted] [redacted] [redacted] [redacted]	15.1 [redacted] [redacted] [redacted] [redacted]	HR 0.776 (0.615, 0.979), p=0.0324
Median OS censored at the start date of the conditioning regimen for HSCT, months	20.8	12.9	HR 0.752 (0.562, 1.008), nominal p=0.055

Endpoint	Quizartinib	Placebo	p-value or HR (95% CI)[a]
Median EFS, months 1-year, % 2-year, % 3-year, %	0.03 [redacted] [redacted] [redacted]	0.71 [redacted] [redacted] [redacted]	HR 0.916 (0.754, 1.114), p=0.2371
Median EFS with ITF defined as not achieving CR by the end of induction up to Day 56 (without a 42-day window), months	5.0	3.4	HR 0.818 (0.669, 0.999), nominal p=0.0323
Median EFS with ITF defined as not achieving CRc by the end of induction up to Day 56 (without a 42-day window), months	11.9	5.7	HR 0.729 (0.592, 0.897), nominal p=0.0031
CR, %	54.9	55.4	NR
CRc, %	71.6	64.9	NR
Median RFS in subjects achieving CRc, months 1-year, % 2-year, % 3-year, %	28.5 68.0 51.9 46.4	12.6 51.8 41.5 39.1	HR 0.733 (0.554, 0.969)
Median RFS in subjects achieving CR, months 1-year, % 2-year, % 3-year, %	39.3 [redacted] [redacted] [redacted]	13.6 [redacted] [redacted] [redacted]	HR 0.613 (0.444, 0.845)
Duration of CR, months	38·6	12.4	HR 0.62 (0.45, 0.86)
Patients undergoing: Protocol-specified HSCT, % Protocol-specified HSCT and non-protocol-specified HSCT, %	38.1 53.7	33.6 47.2	NR NR
Quality of life EQ-5D-5L Index score (UK value set) MMRM for change in score from baseline	Least square mean difference quizartinib vs placebo: [redacted]		

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; CRc, composite complete remission; EFS, event-free survival; HR, hazard ratio; ITF, induction treatment failure; MMRM, mixed-effects model for repeated measures; NR, not reported; OS, overall survival; RFS, relapse-free survival, UK, United Kingdom.
Notes: a. HR with 95% CI for OS and EFS were estimated using stratified Cox regression analysis, while for RFS it was estimated using an unstratified Cox regression analysis. The p-value for EQ-5D-5L index scores and VAS was obtained from an MMRM analysis.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)

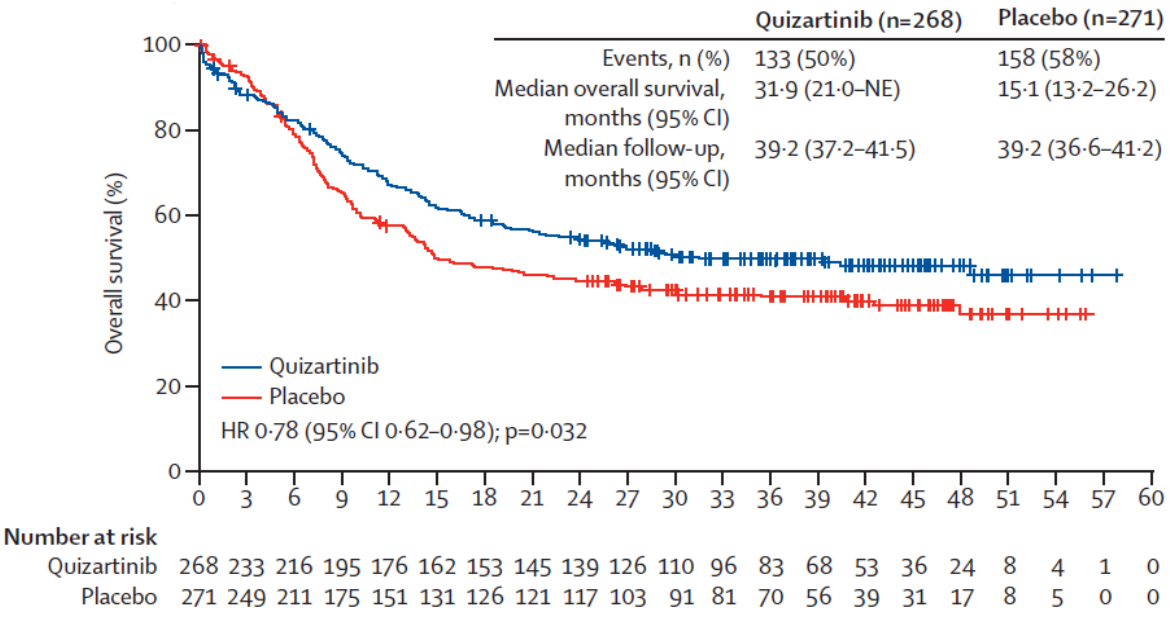
B.2.6.1 Primary efficacy endpoint

Overall Survival

The addition of quizartinib to standard induction and consolidation chemotherapy followed by maintenance with quizartinib monotherapy for up to 3 years, resulted in a statistically significant improvement in OS when compared with placebo with a clear separation of survival curves (Figure 5) (21). The single pivotal trial showed an approximate 10% difference in potential cure rate, as evidenced by the plateaus of the Kaplan-Meier (KM) curves (19).

As of the data cut-off date, the median follow-up time was 39.2 months for both the quizartinib (95% CI: 37.2 to 41.5) and placebo (95% CI: 36.6 to 41.2) arms (21). Median OS was longer in the quizartinib arm (31.9 months; 95% CI: 21.0 to not estimable [NE]) compared with the placebo arm (15.1 months; 95% CI: 13.2 to 26.2), resulting in a 16.8-month prolongation of median OS and a 22.4% relative risk reduction of death (HR: 0.78; 95% CI: 0.62 to 0.98; 2-sided p=0.0324) in favour of the quizartinib arm (Figure 5) (21). The OS rates were also higher for quizartinib vs. placebo at 12, 24, 36 and 48 months (see Table 12) (73). Early deaths are discussed further in section B.2.10.4

Figure 5. Kaplan-Meier plot of overall survival (ITT analysis set)



Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable.
References: Erba et al. 2023 (21)
Notes: Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test. Data cut-off date: 13 Aug 2021

Table 12. Primary analysis of overall survival (ITT analysis set)

Statistics	Quizartinib (N=268)	Placebo (N=271)	Analysis (quizartinib vs. placebo)
Subjects (%) with events (deaths)	133 (49.6)	158 (58.3)	NA
Subjects (%) without events (censored)	[redacted]	[redacted]	NA
Alive at the time of data cut-off date	[redacted]	[redacted]	NA
Withdrawal of consent	13 (4.9)	9 (3.3)	NA
Lost to follow-up	2 (0.7)	1 (0.4)	NA
Hazard ratio (95%CI) [a,c]	NA	NA	0.78 (0.62, 0.98)
2-sided p-value [b,c]	NA	NA	0.0324
Median OS, months (95% CI)[d]	31.9 (21.0, NE)	15.1 (13.2, 26.2)	NA
OS rate (%) (95% CI)[e] at:	NA	NA	NA
6 months	[redacted]	[redacted]	NA
12 months	[redacted]	[redacted]	NA
24 months	[redacted]	[redacted]	NA
36 months	[redacted]	[redacted]	NA
48 months	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NA, not applicable; NE, not estimable; OS, overall survival.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: a. Stratified Cox regression analysis. b. Stratified log-rank test. c. Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old) and WBC count at the time of diagnosis of AML (<40 × 109/L, ≥40 × 109/L). d. Median OS is from KM analysis. CI for median is computed using the Brookmeyer-Crowley method. e. Estimated using the KM method.
Data cut-off date: 13 Aug 2021

OS – supplementary and sensitivity analyses

Unstratified supplementary and sensitivity analyses were conducted to provide supportive evidence for OS results (Table 13) (21).

In the unstratified supplementary analysis of OS, the median OS was [redacted] months in the quizartinib arm and [redacted] months in the placebo arm (HR: [redacted]; 95% CI: [redacted]; nominal [redacted]) (73).

A sensitivity analysis of OS that censored patients who received HSCT at any time during the study was conducted, including both protocol-specified HSCT and non-protocol-specified HSCT (21). Of the 183 (68.3%) subjects in the quizartinib arm and 161 (59.4%) subjects in the placebo arm who were censored in this analysis, 144 (53.7%) subjects in the quizartinib arm and 128 (47.2%) subjects in the placebo arm were censored for HSCT (see section B.2.6.3 for the full transplantation rate results) (21). Results of this analysis showed a median OS of 20.8 (95% CI: 14.3 to 28.9)

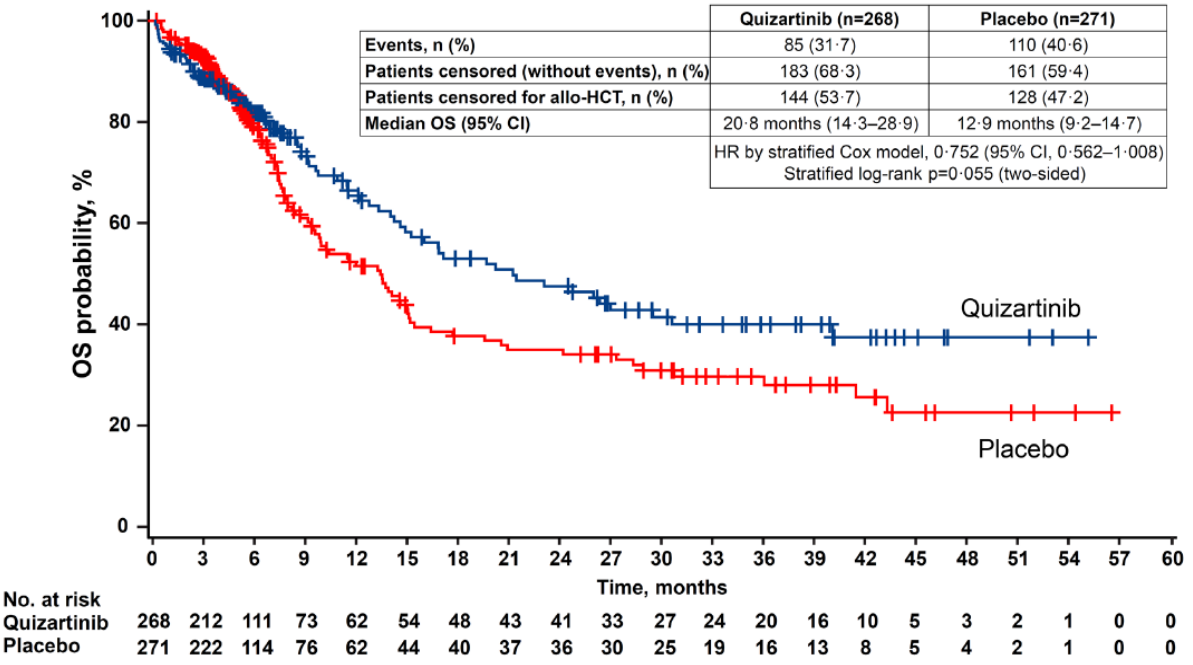
months in the quizartinib arm and 12.9 (95% CI: 9.2 to 14.7) months in the placebo arm (HR: 0.75; 95% CI: 0.56 to 1.01; nominal p=0.055) (21). The corresponding KM plot is presented in Figure 6.

Table 13. Comparison of overall survival using sensitivity and supplementary analyses (ITT analysis set)

Analysis	Median OS (95% CI)[a]		HR relative to placebo (95% CI)	2-sided p-value[b]
	Quizartinib	Placebo		
Primary	31.9 (21.0, NE)	15.1 (13.2, 26.2)	0.78 (0.62, 0.98)[c]	0.0324[c]
Unstratified	[redacted]	[redacted]	[redacted]	[redacted]
Censored at the start date of the conditioning regimen for HSCT	20.8 (14.3, 28.9)	12.9 (9.2, 14.7)	0.75 (0.56, 1.01)[c]	0.0550[c]

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; OS, overall survival.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: a. Median OS was from KM analysis. CI for median was computed using the Brookmeyer-Crowley method. b. Stratified log-rank test. c. Stratification factors included region (North America, Europe, Asia/other regions), age (<60, ≥60 years) and WBC count at the time of diagnosis of AML (<40 × 10^9/L, ≥40 × 10^9/L). d. Log-rank test and Cox PH model were not adjusted for stratification factors.
Data cut-off date: 13 Aug 2021

Figure 6. Kaplan-Meier plot of overall survival censored at the start date of conditioning regimen for HSCT (ITT analysis set)



Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.
References: Erba et al. 2023 (21)
Notes: Data cut-off date: 13 Aug 2021

An additional sensitivity analysis using the restricted mean survival time (RMST) method was conducted to account for a possible plateau effect in OS (73). The RMST survival cut-off time (defined as the smaller of the largest observed survival times in each treatment arm) was [redacted]. The RMST for subjects in the quizartinib arm was [redacted] compared with [redacted] for subjects in the placebo arm. The estimated RMST survival time for subjects who received quizartinib was prolonged by [redacted] which is aligned with the primary analysis (73).

B.2.6.2 Secondary efficacy endpoint

Event-free survival

EFS events were defined as refractory disease (i.e. treatment failure) at the end of the induction phase, relapse or death from any cause (21).

In the original protocol (April 2017), induction treatment failure (ITF) was defined as failure to achieve CR or complete remission with incomplete neutrophil or platelet recovery (CRi) by the end of the induction phase, using an up-to-Day 56 window from the start of the last induction cycle, which is consistent with the clinical practice and the recommendations from current AML guidelines (8, 44, 79). Following a meeting with the US Food and Drug Administration (FDA) on May 2021, the FDA requested to change the ITF definition as failure to achieve CR within 42 days from the start of the last induction chemotherapy. The primary analysis of EFS was consequently updated in the statistical analysis plan to include the FDA-recommended definition of ITF, and the per-protocol definition of EFS was maintained as a sensitivity analysis. An additional analysis was also conducted, using the ITF definition as failure to achieve CR but with the window defined in the original protocol – up-to-Day 56 (21).

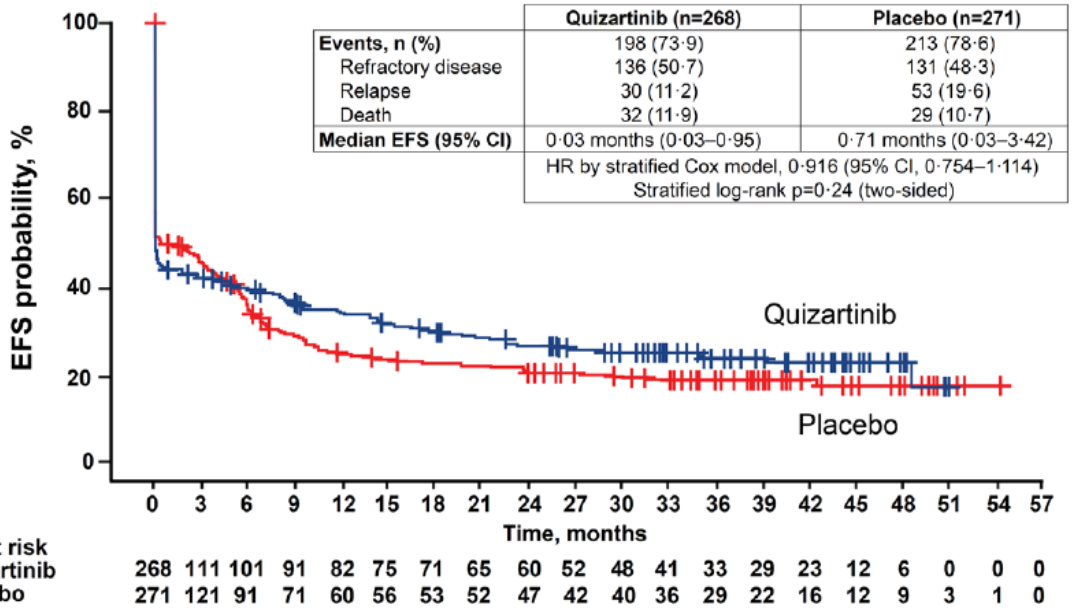
The primary EFS analysis using ITF defined according to the 2020 FDA guidance was assessed by an Independent Review Committee (IRC). A total of 198 (73.9%) subjects in the quizartinib arm and 213 (78.6%) subjects in the placebo arm had an EFS event during the study (21). The median EFS estimated by the KM method was 0.03 (95% CI: 0.03 to 0.95) months in the quizartinib arm and 0.71 (95% CI: 0.03 to 3.42) months in the placebo arm (Figure 7, Table 14). (21). This analysis showed no statistically

significant difference in EFS between subjects in the quizartinib and placebo arms (HR: 0.92; 95% CI: 0.75 to 1.11; 2-sided p=0.24) (Figure 7) (21).

As anticipated, the median EFS values were short in both groups; this is due to the stringent definition of ITF using the 42-day window with event date assigned to Day 1 (i.e. a large number of subjects with true refractory disease and those with CR achieved after Day 42 of their last induction chemotherapy were considered to have EFS events on Day 1). An extended period for assessing CR, as recommended by the current AML guidelines and as assessed in the sensitivity and supplementary EFS analyses, may have allowed patients to recover from quizartinib's myelosuppressive effects. If patients were impacted by myelosuppression in the induction phase, without time to manage it appropriately, it would not have been possible to differentiate patients experiencing the AE from patients with ITF given the method of measurement used for CR.

Given that the main analysis of EFS (using the 42-day window as requested by FDA) was not statistically significant, formal hierarchical testing on other secondary endpoints was not continued (21).

Figure 7. Kaplan-Meier plot of event-free survival with ITF defined as not achieving CR by day 42 from the start of the last induction cycle – IRC assessment (ITT analysis set)



Abbreviations: CI, confidence interval; CR, complete remission; EFS, event-free survival; HR, hazard ratio; ITF, induction treatment failure; ITT, intent-to-treat; IRC, Independent Review Committee.
References: Erba et al. 2023 (21)
Notes: Data cut-off date: 13 Aug 2021

Table 14. Analysis of event-free survival – IRC assessment (ITT analysis set)

Statistics	Quizartinib (N=268)	Placebo (N=271)	Analysis (quizartinib vs. placebo)
Subjects (%) with events	198 (73.9)	213 (78.6)	NA
Refractory disease	136 (50.7)	131 (48.3)	NA
Relapse	30 (11.2)	53 (19.6)	NA
Death	32 (11.9)	29 (10.7)	NA
Subjects (%) without events (censored)	[redacted]	[redacted]	NA
No postbaseline response assessment, no death date	[redacted]	[redacted]	NA
Had CR, no relapse, no death date	[redacted]	[redacted]	NA
Hazard ratio (95% CI)[a,c]	[redacted]	[redacted]	0.92 (0.75, 1.11)
2-sided p-value[b,c]	[redacted]	[redacted]	0.2371
Median EFS, months (95% CI)[d]	0.03 (0.03, 0.95)	0.71 (0.03, 3.42)	NA
EFS rate (%) (95% CI)[e] at:			
2 months	[redacted]	[redacted]	NA
6 months	[redacted]	[redacted]	NA
12 months	[redacted]	[redacted]	NA
18 months	[redacted]	[redacted]	NA
24 months	[redacted]	[redacted]	NA
30 months	[redacted]	[redacted]	NA
36 months	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; CR, complete remission; EFS, event-free survival; IRC, Independent Review Committee; ITT, intent-to-treat; NA, not applicable.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: a. Stratified Cox regression analysis. b. Stratified log-rank test. c. Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old) and WBC count at the time of diagnosis of AML (<40 × 109/L, ≥40 × 109/L). d. Median EFS is from KM analysis. CI for median is computed using the Brookmeyer-Crowley method. e. Estimated using the KM method.
Data cut-off date: 13 Aug 2021

EFS – supplementary and sensitivity analyses

Prespecified EFS sensitivity and supplementary analyses, using ITF definitions consistent with current guidelines from the ESMO, ELN and an International Working Group for AML (8, 44, 79), were conducted. Contrary to the primary analysis, these analyses had nominal p-values of <0.05 and the outcomes showed a benefit of quizartinib over placebo in EFS (21).

For the analysis of EFS using ITF defined as not achieving CR by the end of the induction phase up to Day 56 (rather than using the 42-day window as in the primary analysis), the HR relative to placebo was 0.82 (95% CI: 0.67 to 0.999; nominal

p=0.0323) (21). The median EFS was 5.0 (95% CI: 1.8 to 9.0) months in the quizartinib arm compared with 3.4 (95% CI: 1.7 to 5.5) months in the placebo arm (Table 15, Figure 8) (21).

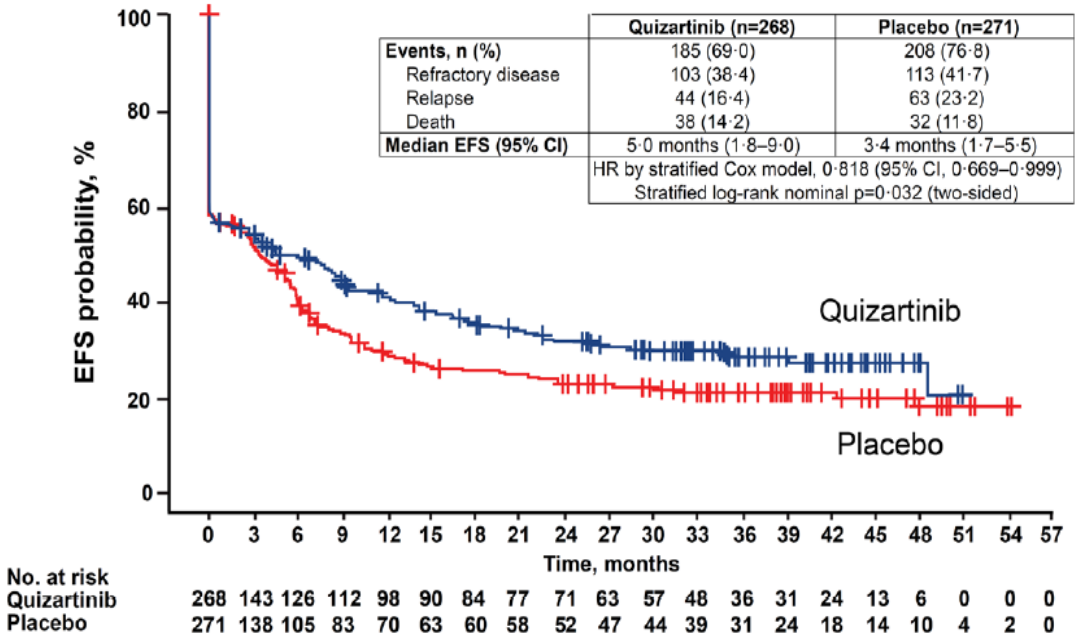
When using the original protocol definition of ITF as not achieving CRc by the end of the induction phase up to Day 56, the median EFS was 11.9 (95% CI: 8.1 to 16.5) months in the quizartinib arm compared with 5.7 (95% CI: 4.0 to 6.9) months in the placebo arm (HR: 0.73; 95% CI: 0.59 to 0.90; nominal p=0.0031) (Table 15, Figure 9) (21).

Table 15. Comparison of event-free survival using sensitivity and supplementary analyses – IRC assessment (ITT analysis set)

Analysis	Median EFS[a] (95% CI)		HR[b] relative to placebo (95% CI)	2-sided p-value[b,c]
	Quizartinib (N = 268)	Placebo (N = 271)		
Primary analysis of EFS – ITF defined as not achieving **CR** by the end of the induction phase, using a **42-day** window from the start of the last cycle in induction for CR evaluation	0.03 (0.03, 0.95)	0.71 (0.03, 3.42)	0.92 (0.75, 1.11)	0.2371
ITF defined as not achieving **CR** by the end of induction up to **Day 56** (without a 42-day window)	5.0 (1.8, 9.0)	3.4 (1.7, 5.5)	0.82 (0.67, 0.999)	0.0323
ITF defined as not achieving **CRc** by the end of induction up to **Day 56** (without a 42-day window[d])	11.9 (8.1, 16.5)	5.7 (4.0, 6.9)	0.73 (0.59, 0.90)	0.0031

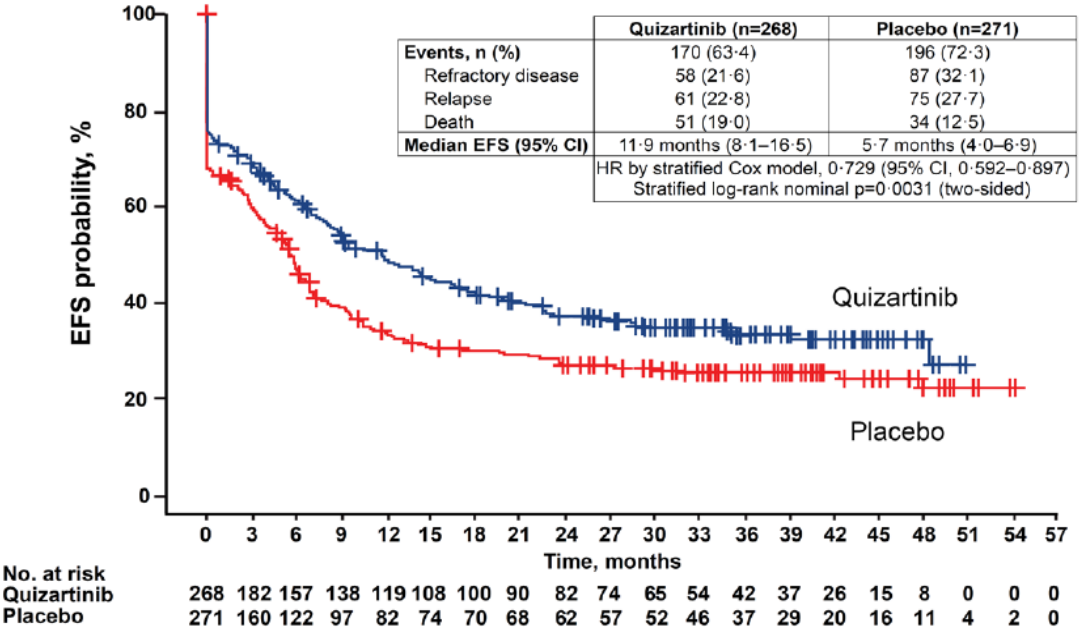
Abbreviations: CI, confidence interval; CR, complete remission; CRc, composite complete remission; EFS, event-free survival; HR, hazard ratio; IRC, Independent Review Committee; ITF, induction treatment failure; ITT, intent-to-treat.
References: Erba et al. 2023 (21)
Notes: a. Median EFS is from KM analysis. CI for median is computed using the Brookmeyer-Crowley method. b. Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old) and WBC count at the time of diagnosis of AML (<40 × 10^9/L, ≥40 × 10^9/L). c. Stratified log rank test. d. original protocol-definition of ITF
Denominator for percentages is the number of subjects in the ITT Analysis Set.
Data cut-off date: 13 Aug 2021

Figure 8. Kaplan-Meier plot of event-free survival with ITF defined as not achieving CR by the end of induction, up to 56 days from the start of the last induction cycle – IRC assessment (ITT analysis set)



Abbreviations: CI, confidence interval; CR, complete remission; EFS, event-free survival; HR, hazard ratio; IRC, Independent Review Committee; ITF, induction treatment failure; ITT, intent-to-treat.
References: Erba et al. 2023 (21)
Notes: Data cut-off date: 13 Aug 2021

Figure 9. Kaplan-Meier plot of event-free survival with ITF defined as not achieving CRc by the end of induction, up to 56 days from the start of the last induction cycle (original protocol-defined primary analysis) – IRC assessment (ITT analysis set)



Abbreviations: CI, confidence interval; CRc, composite complete remission; EFS, event-free survival; HR, hazard ratio; IRC, Independent Review Committee; ITF, induction treatment failure; ITT, intent-to-treat.
References: Erba et al. 2023 (21)
Notes: Data cut-off date: 13 Aug 2021

CR and CRc rates

The initial goal of therapy for AML is control, and as per ELN guidelines whenever possible, eradication of disease; this outcome is accomplished ideally by inducing a CR with initial therapy, followed by consolidation and/or maintenance to deepen the remission and maximize response duration.

Rates of CR at the end of induction were similar between treatment arms (Table 16) and numerically higher CRc (CR + CRi) rates were observed in the quizartinib arm (192 [71.6%] subjects) compared with the placebo arm (176 [64.9%] subjects) (21). These were primarily driven by higher rates of CRi in the quizartinib arm (45 [16.8%] subjects compared with the placebo arm (26 [9.6%] subjects) (21).The higher observed rate of incomplete haematological recovery may be due to the initial myelosuppressive effects of quizartinib in the induction phase and sensitivity of recovery to the time window for response assessment. There is potential for post-marrow blood counts to alter the final response designation [REF 8, ELN]. I.e., potential for complete recovery prior to consolidation therapy.

Table 16. Analysis of other secondary efficacy endpoints: summary of CR rates during induction – IRC assessment (ITT analysis set)

Statistics	Quizartinib (N = 268)	Placebo (N = 271)
CRc (CR + CRi), n (%); 95% CI[a]	192 (71.6); 65.8, 77.0	176 (64.9); 58.9, 70.6
CR, n (%); 95% CI[a]	147 (54.9); 48.7, 60.9	150 (55.4); 49.2, 61.4
CRi[b], n (%); 95% CI[a]	45 (16.8); 12.5, 21.8	26 (9.6); 6.4, 13.7

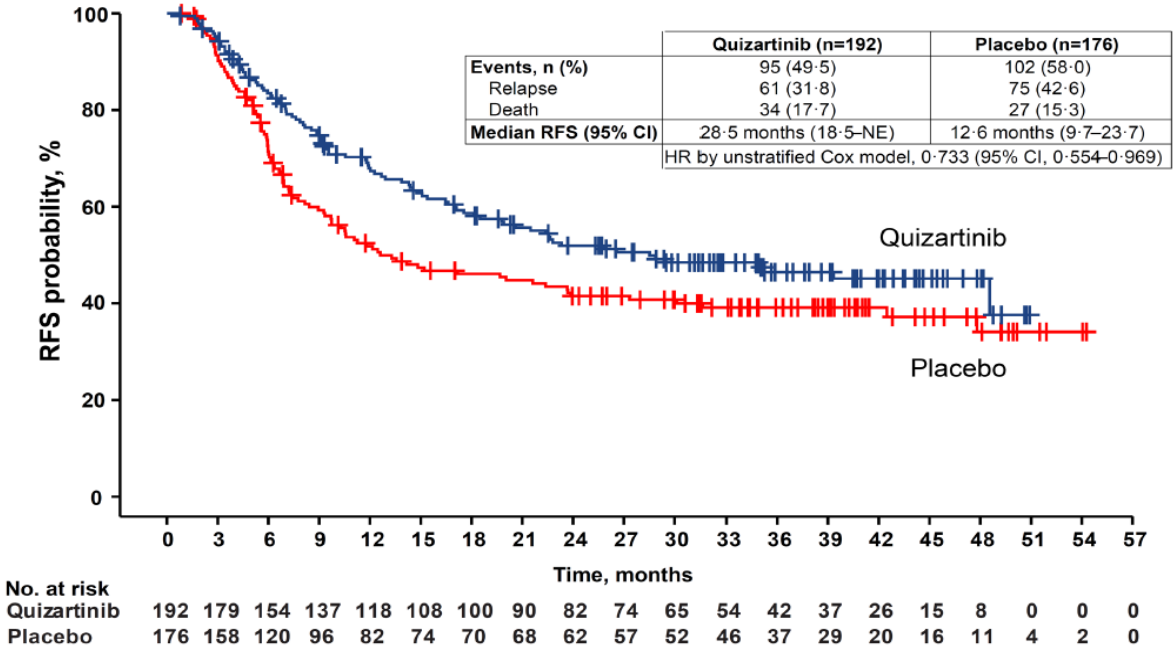
Abbreviations: CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; IRC, Independent Review Committee; ITT, intent-to-treat.
References: Erba et al. 2023 (21)
Notes: Based on assessments by the end of induction (one or two cycles). a. Based on the Clopper-Pearson method. b. CRi was not specified as a secondary endpoint but is included for completeness.
Data cut-off date: 13 Aug 2021

B.2.6.3 Exploratory efficacy endpoints

Relapse-free survival

The median RFS in subjects achieving CRc during the induction phase was 28.5 (95% CI: 18.5 to NE) months in the quizartinib arm and 12.6 (95% CI: 9.7 to 23.7) months in the placebo arm (Table 17). The HR using an unstratified Cox model was 0.733 (95% CI: 0.554 to 0.969) (73). The corresponding KM plot is presented in Figure 10.

Figure 10. Kaplan-Meier plot of relapse-free survival for subjects who achieved CRc in induction phase – IRC assessment (ITT analysis set)



	Quizartinib (n=192)	Placebo (n=176)
Events, n (%)	95 (49·5)	102 (58·0)
Relapse	61 (31·8)	75 (42·6)
Death	34 (17·7)	27 (15·3)
Median RFS (95% CI)	28·5 months (18·5–NE)	12·6 months (9·7–23·7)
	HR by unstratified Cox model, 0·733 (95% CI, 0·554–0·969)	

Abbreviations: CI, confidence interval; CRc, composite complete remission; HR, hazard ratio; IRC, Independent Review Committee; NE, not estimable; RFS, relapse-free survival.
References: Erba et al. 2023 (21)
Notes: Plus symbols indicate censored data. Data cut-off date: 13 Aug 2021

Table 17. Analysis of relapse-free survival for subjects achieving composite complete remission in induction – IRC assessment (ITT analysis set)

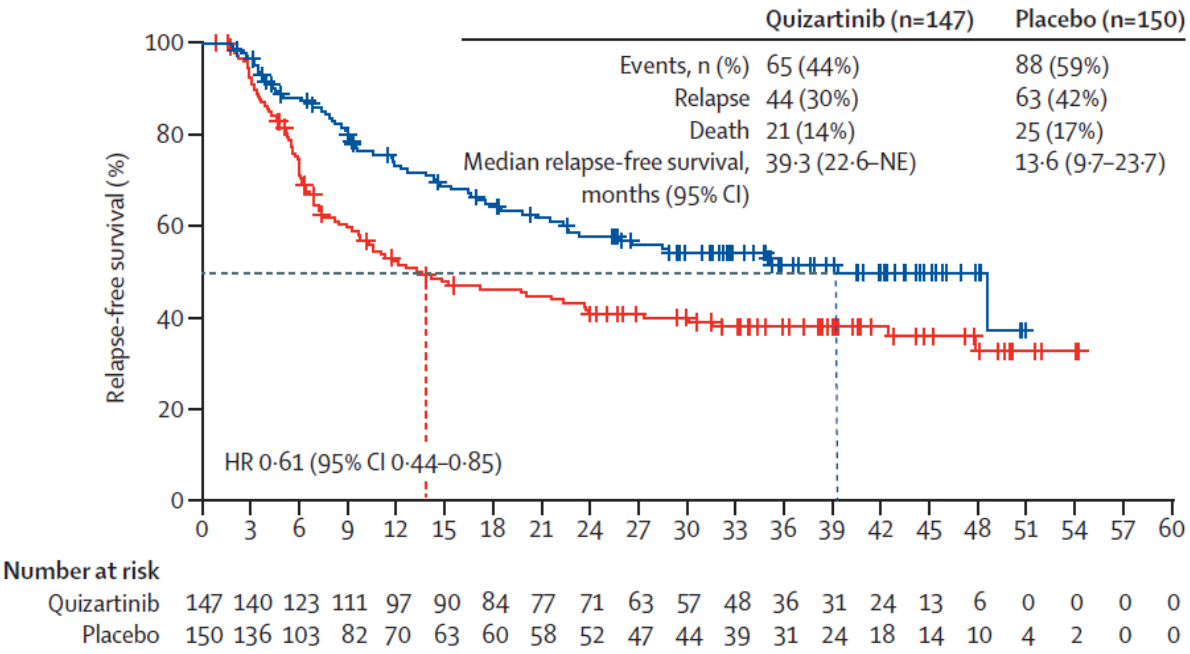
Statistics	Quizartinib (N=268)	Placebo (N=271)	Analysis (quizartinib vs. placebo)
Subjects with CRc (CR+CRi)[a]	192	176	NA
Subjects (%) with events	95 (49.5)	102 (58.0)	NA
Relapse	61 (31.8)	75 (42.6)	NA
Death	34 (17.7)	27 (15.3)	NA
Subjects (%) without events (censored)	[redacted]	[redacted]	NA
Hazard ratio[b] (95% CI)	NA	NA	0.733 (0.554, 0.969)
Median RFS, months[c] (95% CI)	28.5 (18.5, NE)	12.6 (9.7, 23.7)	NA
RFS rate (%)[d] (95% CI) at:			
6 months	[redacted]	[redacted]	NA
12 months	[redacted]	[redacted]	NA
18 months	[redacted]	[redacted]	NA
24 months	[redacted]	[redacted]	NA
30 months	[redacted]	[redacted]	NA
36 months	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; IRC, Independent Review Committee; ITT, intent-to-treat; NA, not applicable; NE, not estimable; RFS, relapse-free survival.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)

Notes: a. Used as denominator for percentage calculation. Subjects without a documented response of CRc are excluded from the analysis. b. Unstratified Cox regression analysis. c. Median RFS is from KM analysis. CI for median is computed using the Brookmeyer-Crowley method. d. Estimated using the KM method.
Data cut-off date: 13 Aug 2021

An additional analysis of RFS was completed which defined RFS as the time from randomisation, for patients who achieved CR (rather than CRc as in the protocol definition of RFS) during induction, until the date of documented relapse or death from any cause, whichever occurred first. Among subjects that achieved CR during the induction phase, median RFS was approximately three times longer with quizartinib (39.3 months [95% CI: 22.6 to NE]) vs. placebo (13.6 months [95% CI: 9.7 to 23.7]) with an HR of 0.61 (95% CI: 0.44 to 0.85) (Figure 11) (21). This RFS benefit was maintained over time (21). The RFS rates were higher for quizartinib vs. placebo at 6, 12, 18, 24, 30 and 36 months (Table 18) (73).

Figure 11. Kaplan-Meier plot of relapse-free survival for subjects who achieved CR in induction phase – IRC assessment (ITT analysis set)



Abbreviations: CR, complete remission; HR, hazard ratio; IRC, Independent Review Committee; ITT, intent-to-treat.
References: Erba et al. 2023 (21)
Notes: Subjects without a documented response of CR are excluded from the analysis
Data cut-off date: 13 Aug 2021

Table 18. Analysis of relapse-free survival for subjects achieving complete remission in induction – IRC assessment (ITT analysis set)

Statistics	Quizartinib (N=268)	Placebo (N=271)	Analysis (quizartinib vs. placebo)
Subjects with CR[a]	147	150	NA
Subjects (%) with events	65 (44.2)	88 (58.7)	NA
Relapse	44 (29.9)	63 (42)	NA
Death	21 (14.3)	25 (16.7)	NA
Subjects (%) without events (censored)	[redacted]	[redacted]	NA
Hazard ratio[b] (95% CI)	NA	NA	0.61 (0.44, 0.85)
Median RFS, months[c] (95% CI)	39.3 (22.6, NE)	13.6 (9.7, 23.7)	NA
RFS rate (%)[d] (95% CI) at:			
6 months	[redacted]	[redacted]	NA
12 months	[redacted]	[redacted]	NA
18 months	[redacted]	[redacted]	NA
24 months	[redacted]	[redacted]	NA
30 months	[redacted]	[redacted]	NA
36 months	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; CR, complete remission; IRC, Independent Review Committee; ITT, intent-to-treat; NA, not applicable; NE, not estimable; RFS, relapse-free survival.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: a. Used as denominator for percentage calculation. Subjects without a documented response of CR are excluded from the analysis. b. Unstratified Cox regression analysis. c. Median RFS is from KM analysis. CI for median is computed using the Brookmeyer-Crowley method. d. Estimated using the KM method.
Data cut-off date: 13 Aug 2021

Duration of CR

Median duration of CR was longer with quizartinib than with placebo (38·6 months, 95% CI: 21.9 to NE vs 12.4 months, 95% CI: 8.8 to 22.7; HR 0.62, 95% CI: 0.45 to 0.86) (Table 19) (21). The duration of CR probability was higher for quizartinib vs. placebo at 6, 12, 18, 24, 30 and 36 months (1) and there was a clear and sustained separation of the curves for up to three years as seen in Figure 12.

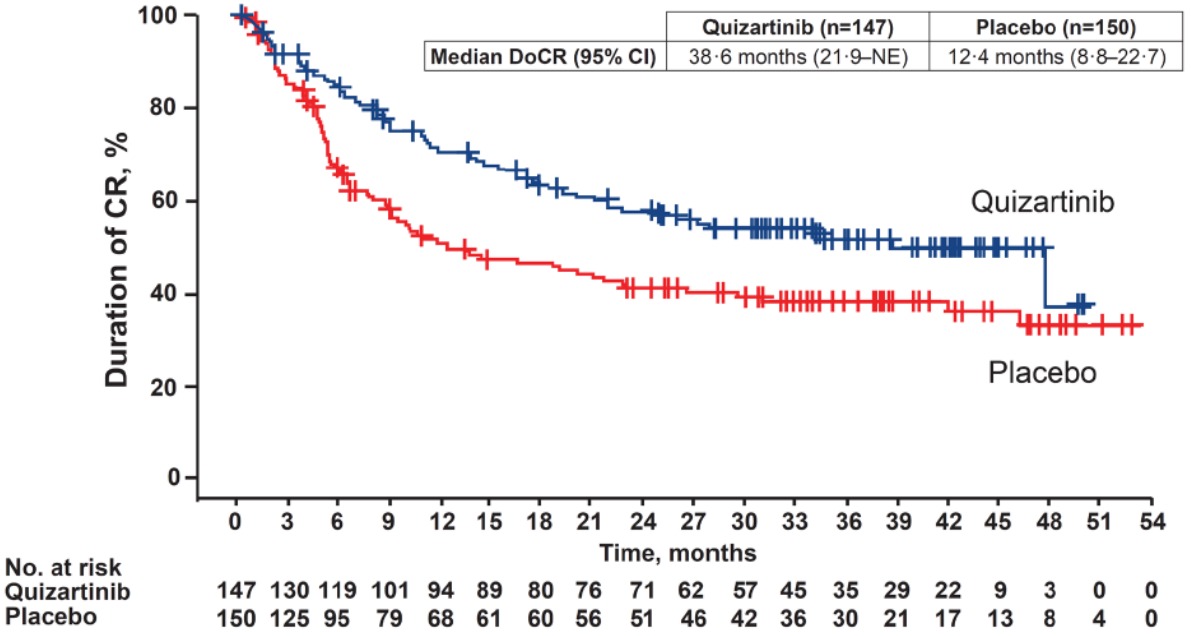
Table 19. Analysis of Duration of Complete Remission – IRC Assessment (ITT Analysis Set)

Statistics	Quizartinib (N=268)	Placebo (N=271)	Analysis (quizartinib vs. placebo)
Subjects with CR (n)	147	150	NA
Median duration of CR (months) (95% CI)[a]	38.6 (21.9, NE)	12.4 (8.8, 22.7)	NA
Hazard ratio (95% CI)	NA	NA	0.621 (0.451, 0.857)
Kaplan-Meier estimated (%) (95% CI) at[b]:			

Statistics	Quizartinib (N=268)	Placebo (N=271)	Analysis (quizartinib vs. placebo)
6 months	[redacted]	[redacted]	NA
12 months	[redacted]	[redacted]	NA
18 months	[redacted]	[redacted]	NA
24 months	[redacted]	[redacted]	NA
30 months	[redacted]	[redacted]	NA
36 months	[redacted]	[redacted]	NA

Abbreviations: CI, confidence interval; CR, complete remission; IRC, Independent Review Committee; ITT, intent-to-treat; NA, not applicable; NE, not estimable
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: Subjects without a documented response of CR are excluded from the analysis. Duration of CR is the time from the first documented CR until the date of documented relapse or death from any cause. a Median duration of CR is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. b Estimated using the Kaplan-Meier method.

Figure 12. Duration of CR in patients who achieved CR during induction



Abbreviations: CR, complete remission; DoCR, duration of complete remission
References: Erba et al. 2023 (76)

Transplantation rate

During the study, subjects were permitted to undergo HSCT after CR or CRi was achieved. Protocol-specified HSCT was to be performed after the induction phase or anytime during the consolidation phase or, if certain protocol-defined criteria were met,

HSCT was also permitted during the continuation phase[1]. Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens). Any HSCT performed that did not meet these criteria or performed for other reasons, e.g. molecular relapse, were considered non-protocol-specified AML therapy. A total of 102 (38.1%) subjects in the quizartinib arm and 91 (33.6%) subjects in the placebo arm underwent protocol-specified HSCT (1). A further 15.6% and 13.6% of subjects received non-protocol specified HSCT in the quizartinib and placebo arms respectively (Table 20) (21, 73).

Table 20. HSCT rate (ITT analysis set)

	Quizartinib (N=268)	Placebo (N=271)
Protocol-specified HSCT[a], n (%) [95% CI][b]	[redacted]	[redacted]
Protocol-specified HSCT and non-protocol-specified HSCT[c], n (%)	144 (53.7)	128 (47.2)

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; HSCT, hematopoietic stem cell transplantation; ITT, intent-to-treat.
References: Daiichi Sankyo, 2022 (73) Erba et al. 2023 (76)
Notes: a Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens). b Based on the Clopper-Pearson method. c. Any HSCT performed for other reasons, e.g. molecular relapse, will be considered non-protocol-specified AML therapy, and the subject will be discontinued from quizartinib or placebo but will continue to be followed for outcome data.
Denominator for percentages is the number of subjects in the ITT Analysis Set.
Data cut-off date: 13 Aug 2021

Quality of life

PROs for exploratory purposes were collected using EuroQoL EQ-5D-5L and European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQ-C30) in the QuANTUM-First study (75). Both the EQ-5D-

[1] A subject is permitted to undergo HSCT for consolidation after the start of the maintenance phase if the following criteria are met
- When the subject starts the consolidation phase, the plan is for the subject to undergo HSCT as part of consolidation therapy
- A donor is not able to be found during the consolidation phase but becomes available after the start of the maintenance phase
- The investigator discusses the case with the Medical Monitor
- Confirmed <5% of blasts based on the most recent bone marrow aspirate, based on the local laboratory results
- The transplant is performed within 3 months after Day 1 of maintenance therapy.

5L and EORTC-QLQ-C30 yielded similar results. EQ-5D-5L Index Score for the UK is considered the most relevant outcome for this apprised and is summarised below.

The EQ-5D-5L scores were collected at each trial visit for both treatment arms. The current study is the first study to explore the impact of quizartinib on QoL for adult patients with *FLT3-ITD+* AML, although the study was not designed to formally compare the treatment impact of quizartinib on PRO measures to that of placebo when combined with standard chemotherapy. As such, it provides an interesting insight into trends in QoL within this patient population. Overall, the completion rates for both QoL scales were high and patients in both arms reported similar QoL scores at PRO baseline. After treatment initiation, most QoL scales improved over time in both arms. Minimal differences were observed between the two treatment arms in score changes from baseline and were not statistically significant as seen in the longitudinal model (mixed-effects model for repeated measures [MMRM]).

For the majority of QoL scales, consistent improvement beyond the minimal clinically important difference (MCID) threshold was reported over time (from induction phase or during continuation phase, depending on the scale).

Given the exploratory nature of the PRO analyses, the results should be interpreted carefully.

A total of 509 patients were included in the PRO analysis set (254 and 255 patients in the quizartinib and placebo arms, respectively) (75). The UK value set for the index score were calculated using the mapping function introduced by Hernández-Alava (80) as recommended in the NICE manual for health technology evaluations (81).

EQ-5D-5L Index Score (UK value set)

Among the 509 patients in the PRO analysis set, [redacted] had a completed EQ-5D-5L index score at PRO baseline (induction phase Cycle 1 Day 8) (UK value set) (75). The scores at PRO baseline were similar between treatment arms, with mean (standard deviation [SD]) EQ-5D-5L index scores of [redacted] in the quizartinib arm vs. [redacted] in the placebo arm (75). The compliance rate by visit ranged from [redacted] to [redacted] and [redacted] to [redacted] for the quizartinib and placebo arms respectively (75).

An MMRM analysis was performed adjusting for score at baseline, treatment, time and a treatment-by-time interaction (Figure 13) (75). It shows the change from PRO baseline effect of quizartinib vs. placebo on the EQ-5D-5L index score (UK value set) over time. The results demonstrate an improvement in EQ-5D-5L index score (UK value set) over time in both treatment arms compared to PRO baseline results. Improvement was on average greater than the MCID (an increase of 0.06) from treatment initiation through maintenance Cycle 34 Day 1 in both arms as can be seen in Figure 13. No meaningful difference in EQ-5D-5L score was observed between quizartinib and placebo, with a least-squares mean difference of [redacted] (75).

Figure 13. EQ-5D-5L UK index score (Hernández Alava) - Plot of Least Square Means estimate by treatment across time

Abbreviations: C, cycle; CI, confidence interval; D, day; EuroQoL-5D-5L; UK, United Kingdom.
References: Daiichi Sankyo, 2022 (75)
Notes: a. Least Square Means and associated Confidence Interval from Mixed Model Repeated Measures: Changes in the QoL scores = Baseline + Treatment + Time + Treatment x Time b. Structure of covariance matrix: Autoregressive (AR). c. For EQ-5D-5L index (UK value set), a more than MCID increase is considered 'improved', a more than MCID decrease is considered 'worsened', a change between -MCID and MCID (inclusive) is considered 'stable'. For EQ-5D-5L index (UK value set), MCID is 0.06.

B.2.6.4 Post-hoc analyses

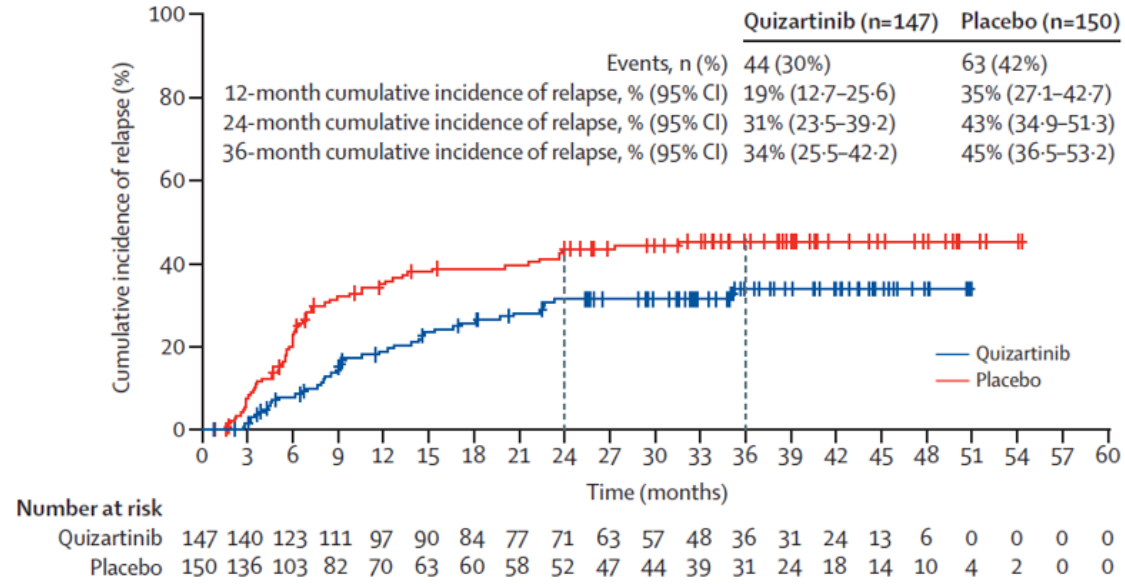
A post-hoc analysis (data cut-off: August 13, 2021) was conducted in 308 (84%) of the 368 patients with CRc after induction (21). For this analysis variant allele frequencies (VAF) were calculated with a sensitivity of 1×10^{-5} leukaemia cells and minimal or measurable residual disease (MRD) negativity was classified using two cut-offs: < 1 x 10^{-4} and 0 (82). MRD assessment in AML is used to provide a quantitative methodology of prognostic value to assess a deeper remission status and to identify impending relapse (8).

Among the 157 patients with CRc treated with quizartinib after induction, 66 (42%) had MRD negativity (less than 10^{-4} leukaemia cells) versus 58 (38%) among the 151 patients with CRc treated with placebo as assessed at the time of CR or CRi (21). Although *FLT3-ITD* MRD is not yet a validated surrogate marker for OS in routine practice, the MRD data may suggest that the addition of quizartinib to chemotherapy results in a deeper response at the end of induction.

While the overall proportion of patients with CRc with *FLT3-ITD* MRD negativity (less than 10^{-4}) was similar across groups (66 [25%] of 268 in the quizartinib group vs. 58 [21%] of 271 in the placebo group), the proportion of patients with CRc with undetectable MRD (by use of the 0 cut-off) was larger with quizartinib (37 [14%] of 268 vs. 20 [7%] of 271) (21). Among patients who achieved a CRc after induction, the median *FLT3-ITD* MRD VAF was three times lower with quizartinib (0·01%, interquartile range [IQR]: 0·00-0·182) than with placebo (0·03%, IQR: 0·00–0·26) (21, 82).

A post-hoc analysis was also performed to analyse the cumulative incidence of relapse (CIR) from randomisation in subjects who achieved a CR during the induction phase treating death prior to relapse as a competing risk (21). The CIR rates were numerically lower in the quizartinib arm than the placebo arm at 12 months, 24 months and 36 months (Figure 14) suggesting that quizartinib might prevent or delay relapses (21).

Figure 14. Cumulative incidence of relapse in patients with complete remission during induction – IRC assessment (ITT analysis set)



Abbreviations: CI, confidence interval; IRC, Independent Review Committee; ITT, intent-to-treat.
References: Erba et al. 2023 (21)
Data cut-off date: 13 Aug 2021

B.2.7 Subgroup analysis

For QuANTUM-First, as described in Table 5, pre-planned subgroup analyses of two efficacy outcomes, OS and EFS, were conducted based on (21):

- Demographic characteristics:
  - Age
  - Sex
  - Race
  - Geographical region
- Baseline disease characteristics:
  - ECOG performance status
  - WBC count at the time of diagnosis
  - Choice of anthracycline used during the induction phase
  - AML cytogenetic risk score
  - *FLT3-ITD* VAF at randomisation
  - *NPM1* mutational status.

A list of analysed subgroups is presented in Table 5 and a summary of the results for the subgroup analyses is provided in Appendix E.

Both the pre-planned and post-hoc efficacy subgroup analyses were performed similarly to the primary analyses of OS and EFS (Table 9), except the analyses were performed without stratification and p-values were not reported (21). When the total number of subjects in any subgroup category was fewer than 30, no analysis for that category was performed and only the number of subjects and number of events for each treatment in that category were summarised (73). If the total number of subjects in any subgroup category was fewer than five, no summary for that category was provided (73).

For safety subgroup analyses, pre-defined subgroup analyses of TEAEs were performed based on:

- Demographic factors:
    - Age
    - Sex
    - Race
- Choice of anthracycline used during the induction phase.

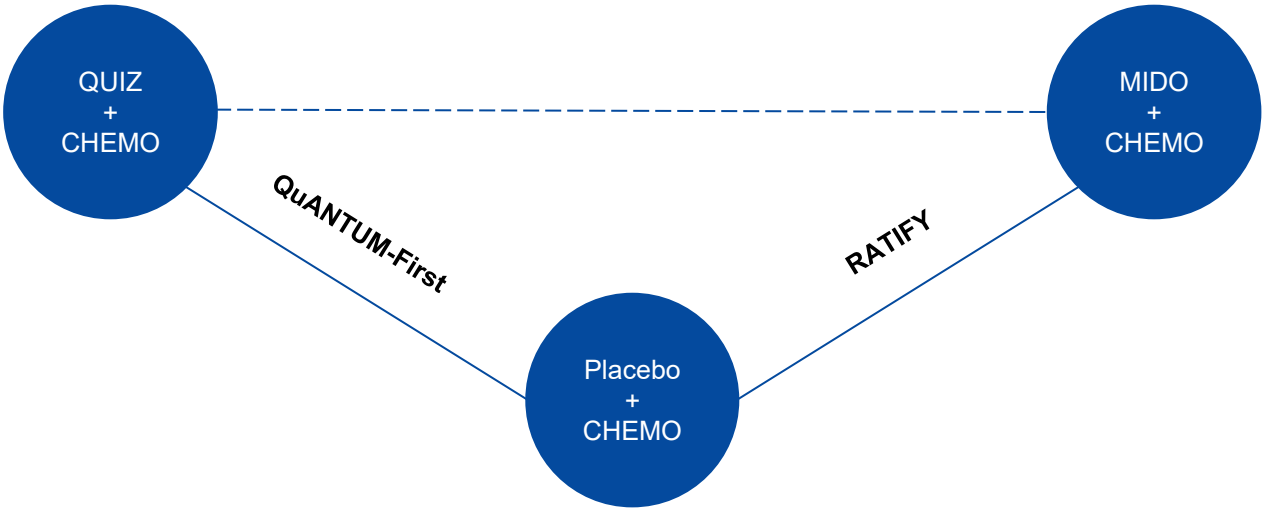
Another pre-planned subgroup analysis was performed to evaluate the effects of age, sex, use of strong CYP3A4 inhibitors and use of medications to prolong the QT on electrocardiogram (ECG) results. Safety subgroup analyses results were only summarised descriptively (73).

B.2.8 Indirect treatment comparisons

B.2.8.1 Objective of the indirect comparison

Midostaurin is considered the most relevant comparator for quizartinib as explained in the decision problem section (B.1.1) and the treatment guidelines section (B.1.3.4). An SLR was conducted to assess the available clinical evidence base of current first-line treatments in patients with *FLT3-ITD*+ AML. Details of the search strategy and results of the SLR are provided in Appendix D. No head-to-head trials of quizartinib vs. midostaurin were identified and consequently an indirect treatment comparison (ITC) was required to estimate the relative efficacy of quizartinib vs. midostaurin. The SLR identified two studies suitable for the ITC: QuANTUM-First (NCT02668653) as the relevant randomised trial evaluating the efficacy of quizartinib and RATIFY (NCT00651261) for midostaurin. The quality assessments for QuANTUM-First and RATIFY can be found in section B.2.5 and Appendix D. Based on the network diagram (Figure 15) of the treatments in each of the trials and the NICE Decision Support Unit (DSU) technical support document (TSD) 18 (83), an anchored ITC, with placebo + standard induction and consolidation chemotherapy as the anchor, was considered suitable to analyse the relative efficacy of quizartinib vs. midostaurin. A feasibility assessment was then conducted to determine what type of ITC methodology was suitable, if any.

Figure 15. Network diagram of the ITC comparing quizartinib and midostaurin



Abbreviations: CHEMO, chemotherapy; MIDO, midostaurin; QUIZ, quizartinib.

B.2.8.2 Assessment of study heterogeneity

Prior to conducting the ITC analyses, a feasibility assessment was performed to assess whether there was heterogeneity between the studies in terms of trial characteristics, outcome definitions and patient baseline characteristics.

Trial characteristics

Comparisons of trial characteristics (Table 21) revealed heterogeneity between the QuANTUM-First and RATIFY populations. Most evidently, RATIFY included patients with either *FLT3-ITD* or *FLT3-TKD* mutations, whereas QuANTUM-First's population consisted of patients with a *FLT3-ITD* mutation only. To enable a meaningful comparison, a subgroup analysis of RATIFY published by Rucker et al. which included only patients with a *FLT3-ITD* mutation (63.04% of the ITT population) (84), was used in the ITC. In addition, QuANTUM-First enrolled patients aged 18-75 years whereas the RATIFY study enrolled patients aged 18-59 years. To allow for a better alignment between the trial populations, only individual patient data (IPD) of patients aged <60 years from the QuANTUM-First population was used in this analysis. In QuANTUM-First, the randomisation is stratified by age (<60, ≥60 years old), therefore, restricting the population to patients under 60 years old maintains randomisation of the QuANTUM-First trial data.

In terms of interventions, patients in QuANTUM-First could receive either daunorubicin or idarubicin for induction, compared to those in RATIFY who could only receive daunorubicin in this phase. While the choice of anthracycline in QuANTUM-First was broader, chemotherapy options were considered equivalent between the studies. Patients in QuANTUM-First were stratified based on their age, region and WBC count, whilst those in RATIFY were stratified by *FLT3* mutation subtype (i.e. *TKD*, *ITD* with low allelic ratio [<0.5] and *ITD* with high allelic ratio [>0.5]) (10), which may have resulted in different distributions of baseline characteristics across the two trials. Treatment with a second induction following residual disease after first induction was composed of '7+3' chemotherapy regimen in RATIFY, while either '7+3' or '5+2' were allowed in QuANTUM-First. Clinical validation indicated this would not have impacted the efficacy of chemotherapy (85).

Table 21. Trial characteristics of QuANTUM-First and RATIFY

Characteristic	QuANTUM-First	RATIFY
Population	Newly diagnosed *FLT3-ITD*+ AML patients aged 18-75	Newly diagnosed *FLT3*+ AML patients aged 18-59
Treatment line	1L	1L
Intervention[a]	**Induction:** quizartinib + standard induction chemotherapy (cytarabine + daunorubicin or idarubicin) **Consolidation:** 1) Quizartinib + standard consolidation chemotherapy (high-dose cytarabine) 2) HSCT 3) Quizartinib + standard consolidation chemotherapy (high-dose cytarabine) and HSCT **Maintenance:** quizartinib for up to 36 cycles of 28 days (three years)	**Induction:** midostaurin + standard induction chemotherapy (cytarabine + daunorubicin) **Consolidation**: midostaurin + standard consolidation chemotherapy (high-dose cytarabine) **Maintenance:** midostaurin for up to 12 months Transplantation was not mandated in the protocol but was performed at the discretion of the investigator.
Comparator[a]	**Induction:** placebo + standard induction chemotherapy (cytarabine + daunorubicin or idarubicin) **Consolidation:** 1) Placebo + standard consolidation chemotherapy (high-dose cytarabine) 2) HSCT 3) Placebo + standard consolidation chemotherapy (high-dose cytarabine) and HSCT **Maintenance:** placebo	**Induction:** placebo + standard induction chemotherapy (cytarabine + Daunorubicin) **Consolidation:** placebo + standard consolidation chemotherapy (high-dose cytarabine) **Maintenance:** placebo Transplantation was not mandated in the protocol but was performed at the discretion of the investigator.
Outcomes[b]		
Primary endpoint	OS	OS
Secondary endpoints	EFS, CR rate and CRc rate after induction, percentage of subjects achieving CR and CRc with *FLT3-ITD* MRD negativity following induction therapy	EFS, HSCT censored OS, CR rate, DFS, HSCT rate
Study design		

Characteristic	QuANTUM-First	RATIFY
Randomisation	1:1, stratified by age, region and WBC count	1:1, stratified by *FLT3* subtypes (*TKD*, ITD_{low} *or* ITD_{high})
Blinding	Double-blinded	Double-blinded
Prior & Concomitant Therapy	No prior or concomitant therapy, with some exceptions[c]	No prior or concomitant therapy, with some exceptions[c]
Median follow-up time (months)	39[d]	59[d]
Sample size	539	717 (*FLT3-ITD*: 555, *FLT3-TKD*: 162)

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; AR, allelic ratio; CR, complete remission; CRc, composite complete remission; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; *FLT3*, FMS-like tyrosine kinase 3; HSCT, hematopoietic stem cell transplant; *ITD*, internal tandem duplication; ITT, intent-to-treat; MRD, minimal or measurable residual disease; OS, overall survival; TBL, total bilirubin; *TKD*, tyrosine kinase domain; WBC, white blood cell; 1L, first-line.
References: Erba et al. 2023 (21); Stone et al., 2017 (10)
Notes: a. In the first induction cycle, '7+3' was used in both trials; in the second induction cycle, both '7+3' and '5+2' were allowed in QuANTUM-First, while only '7+3' was used in RATIFY. High-dose cytarabine was used in the consolidation phase of both trials, with the exception of patients ≥60 years in QuANTUM-First who received an intermediate dose of cytarabine. b. Exploratory endpoints are described in section B.2.2 c. Exceptions were aligned across the two trials d. The figure presented for QuANTUM-First refers to the median follow-up time for the ITT population whereas the figure presented for RATIFY relates to the median follow-up time amongst patients that survived.

Outcome definitions

The ITCs compared OS, CR and CIR (as a proxy of RFS) outcomes between QuANTUM-first and RATIFY. It was not feasible to compare other endpoints, such as RFS because RFS in QuANTUM-First used the date from randomisation as the start date whilst the equivalent outcome in RATIFY (DFS) used the date at which CR was achieved as the start date of analysis.

The definition of OS was consistent across both trials (Table 22). The definitions of CR were largely aligned across the trials. QuANTUM-First counted any CR achieved within the two induction cycles, encompassing a period up to 120 days[2]. Similarly, RATIFY counted CR until Day 60 from randomisation, but allowed a second induction cycle and attributed any CR to the initial 60 days, effectively also considering any CR within 120 days. The definition of CIR was not clearly described in RATIFY introducing some uncertainty. Assuming CIR is defined as the proportion of patients experiencing relapse after achieving CR, the relative components of this definition (i.e. CR and relapse) were similarly defined between the trials. However, the definitions of relapse after CR, which impacts CIR, differed slightly with the 'presence of Auer rods' also indicating relapse in QuANTUM-First but not in RATIFY.

[2] According to the clinical trial protocol the second induction cycle was permitted to start up to 60 days after Day 1 of the first Induction cycle and had a duration of up to 59 days.

Table 22. Comparison of common outcomes employed in QuANTUM-First and RATIFY trials

Outcome	QuANTUM-First	RATIFY
OS	Time from randomisation until death from any cause. Subjects alive or lost to follow-up at the time of analysis were censored at the date when they were last known to be alive.	The period from the date of randomisation until death by any cause. Patients who were alive at the end of study period were censored for this endpoint.
CR	CR (IRC response criteria) was defined as (all criteria should be met): • Neutrophils >1,000 cells/mm^3 • Platelets >100,000 platelets/mm^3 • Bone marrow blasts <5% • Other requirements: absence of extramedullary disease, absence of blasts with Auer rods, absence of leukemic blasts in the peripheral blood by morphological examination. A 120 days cut-off was used	CR in RATIFY was assessed by bone marrow examination and defined as: • An ANC of at least 1,000 per microlitre • A platelet count of at least 100,000 per microlitre • The presence of less than 5% blasts in the marrow or extramedullary leukaemia • The absence of blasts in the peripheral blood. Per protocol, complete remission had to occur by day 60 but also included CR during a second induction cycle effectively adding up to 120 days
CIR	CIR from the time of achievement of CR in all subjects who achieved a CR in the induction phase treating death prior to relapse as a competing risk.	CIR (for patients who have achieved CR after study treatment initiation), is measured from the date of first CR to relapse or death due to AML, whichever occurs first. Relapse among patients achieving a CR treating death as a competing risk.
	Relapse after CR was defined as: • ≥5% blasts in the bone marrow aspirate and/or biopsy not attributable to any other cause; or • Reappearance of leukemic blasts in the peripheral blood; and/or • New appearance of extramedullary leukaemia; or • Presence of Auer rods.	Relapse after CR was defined as: • >5% blasts in the marrow, not attributable to another cause (e.g. CSF and bone marrow regeneration); or • The reappearance of circulating blast cells not attributable to 'overshoot' following recovery from myelosuppressive therapy; or • Development of extramedullary leukaemia.

Abbreviations: AML, acute myeloid leukaemia; ANC, absolute neutrophil count; CIR, cumulative incidence of relapse; CR, complete remission; CSF, cerebrospinal fluid; IRC, Independent Review Committee; OS, overall survival.
References: Daiichi Sankyo, 2022 (73); Stone et al. 2017 (10)

Patient baseline characteristics

There were several differences noted in the baseline characteristics of patients enrolled in the two trials. The mean age of the QuANTUM-First population was older due to the trial eligibility criteria as described in the previous section (Table 23). Additionally, QuANTUM-First's patient population demonstrated a lower median platelet count compared to that of RATIFY. Of the patients in RATIFY that had the *FLT3-ITD* mutation a higher proportion had a high allelic ratio (<0.5) of the mutation (midostaurin arm: 65.2%, placebo arm: 63.4%) compared to QuANTUM-First (quizartinib arm: 49.25%, placebo arm: 47.23%). Furthermore, whilst the proportion of patients with *NPM1* mutations was aligned across the treatment arms of both studies and the placebo arm of the QuANTUM-First study, a comparatively higher proportion of patients in the placebo arm of the RATIFY study was noted. Characteristics that could not be assessed for similarity across the studies due to reporting limitations in both trials were ECOG performance status, demographic region of patients, WBC count, ELN and cytogenetic risk, karyotypes and CCAAT/enhancer binding protein α (*CEBPA*) mutations.

Table 23. Baseline characteristics of patients included in QuANTUM-First and RATIFY

Characteristics	QuANTUM-First		RATIFY	
	FLT3-ITD (ITT)		*FLT3-ITD*[d]	
	Quizartinib (N=268)	Placebo (N=271)	Midostaurin (N=230)	Placebo (N=222)
Median age (range), years	56 (23, 75)	56 (20, 75)	47 (19, 59)	48 (18, 60)
Sex, male, n (%)	124 (46.3)	121 (44.6)	114 (49.6)	92 (41.4)
Race, n (%)				
White	159 (59.3)	163 (60.1)	NR	NR
Other	27 (10.1)	24 (8.9)	NR	NR
Asian	80 (29.9)	78 (28.8)	NR	NR
Black or African American	2 (0.7)	5 (1.8)	NR	NR
Subtype of *FLT3* mutation, n (%)[a]				
FLT3-ITD with low allelic ratio (<0.5)	[redacted]	[redacted]	80 (34.8)	81 (36.6)
FLT3-ITD with high allelic ratio (>0.5)	[redacted]	[redacted]	149 (65.2)	141 (63.4)
2017 ELN risk group, %[b]				
Favourable	NR	NR	25.2[e]	32.3[e]
Intermediate	NR	NR	33.3[e]	37.6[e]
Adverse	NR	NR	41.5[e]	30.1[e]
Risk status with specific cytogenetic patterns, n (%)[c]				
Favourable	14 (5.2)	19 (7.0)	NR	NR
Intermediate	197 (73.5)	193 (71.2)	NR	NR
Adverse	19 (7.1)	27 (10.0)	NR	NR
Unknown	38 (14.2)	21 (11.4)	NR	NR
Karyotype, n (%)				
Normal	NR	NR	107 (62.2)[e]	141 (80.1)[e]
Abnormal	NR	NR	65 (37.8)[e]	35 (19.9)[e]
***NPM1* mutation n, (%)**	142 (53.0)	140 (51.7)	95 (50.0)[e]	108 (64.3)[e]
Median platelet counts 10^3/µL (range)	[redacted]	[redacted]	51 (2, 461)	50 (8, 342)
Median ANC per mm^3 (range)	[redacted]	[redacted]	NR	NR
WBC count at diagnosis of AML				
<40 × 10^9/L, n (%)	135 (50.4)	137 (50.6)	NA	NA
≥40 × 10^9/L, n (%)	133 (49.6)	134 (49.4)	NA	NA
Median (range), 10^9/L	NA	NA	42.6 (0.8, 304)	42.1 (0.8, 329.8)
Median bone marrow blast count (range), n	[redacted]	[redacted]	77 (3, 100)	80 (6, 100)

Abbreviations: ANC, absolute neutrophil count; AML, acute myeloid leukaemia; ELN, European LeukemiaNet; *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; ITT, intent-to-treat; NA, not applicable; NR, not reported; *NPM1*, nucleophosmin 1; WBC, white blood cell.
References: Erba et al. 2023 (21); Daiichi Sankyo, 2022 (73); Rucker et al., 2021 ; Döhner et al., 2017(43)
Notes: a. The *FLT3* subtype of one patient (0.4%) in the quizartinib group was unknown/could not be determined. b. 2017 ELN guidelines stratified risk according to the genetic abnormality (including FLT3) identified at screening and categorised it into three groups: favourable, intermediate and adverse. Favourable: t(8;21)(q22;q22.1); *RUNX1-RUNX1T1,* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11,* mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD^{low}*, biallelic mutated *CEBPA;* intermediate: mutated *NPM1* and *FLT3-ITD^{high}*, wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD^{low}* (without adverse-risk genetic lesions), t(9;11)(p21.3;q23.3); *MLLT3-KMT2A,* cytogenetic abnormalities not classified as favourable or adverse; adverse: t(6;9)(p23;q34.1); *DEK-NUP214,* t(v;11q23.3); *KMT2A* rearranged, t(9;22)(q34.1;q11.2); *BCR-ABL1,* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*,*MECOM(EVI1),* −5 or del(5q);

−7; −17/abn(17p), complex karyotype, monosomal karyotype, wild-type *NPM1* and *FLT3-ITD*^{high}, mutated *RUNX1,* mutated *ASXL1,* mutated *TP53.* c. Favourable: inv(16), t(16;16), t(8;21), t(15;17); intermediate: normal, +8, +6, -y; unfavourable: del5q, -5, del7q, -7, complex. d. Baseline characteristics for RATIFY's *FLT3-ITD* subgroup retrieved from the Rucker et al. publication (84). Selected by means of available next-generation sequencing samples, the analysed study population covered a sample of 81% of *FLT3-ITD*+ patient population in RATIFY, which a clinical expert indicated is likely representative of the entire *FLT3-ITD*+ patient population in RATIFY. e. Data was not available for the full sample in these instances: 1. 2017 ELN risk group, midostaurin arm sample size: 135; placebo arm sample size: 133. 2. Karyotype, midostaurin arm sample size: 172; placebo arm sample size:176. 3. *NPM1* mutation, midostaurin arm sample size: 190; placebo arm: 168.

B.2.8.3 Determination of treatment effect modifiers

Rationale

Given the feasibility assessment highlighted potential heterogeneity in a number of patient characteristics, a population adjustment using an anchored matching adjusted treatment indirect comparison (MAIC) was considered for the ITC. The adoption of a MAIC over a standard unadjusted ITC should be justified with evidence that all parameters adjusted for are treatment effect modifiers (TEMs) or that the degree of imbalance in characteristics between the trials causes a material difference in the outcomes of interest per the NICE DSU TSD 18 (83). A TEM is any variable that alters the effect of treatment on relative outcomes, such that the treatment is more or less effective in different subgroups. In contrast, prognostic variables influence the outcome but not the treatment effect. Randomisation within each trial ensured that bias due to imbalanced prognostic variables across the trials was omitted. However, baseline characteristics that modify the effect of treatment (i.e. TEMs) cannot be controlled through randomisation and therefore have the potential to introduce bias into the estimated relative treatment effect if the data is not adjusted to accounted for these e.g. via a MAIC. Firstly, it was necessary to confirm the presence of TEMs to determine whether a MAIC was an appropriate methodology for the ITC.

Potential TEMs were first identified by reviewing the literature (i.e. trial publications and subgroup data). Then a quantitative assessment using interaction analysis of QuANTUM-First trial data was conducted. The final list of TEMs included in the MAIC were selected through discussion with three clinical experts.

Literature review for potential TEMs in RATIFY

Subgroup analyses presented in the publications of the RATIFY trial were evaluated for the reporting of clinical subgroups across which the treatment effect varied. RATIFY subgroup analyses were only available for the OS outcome and included an

assessment of sex, age, *FLT3* subtype, ELN risk, *NPM1* mutation status and WBC count. Out of the analysed selection, age, *NPM1* mutation status and ELN risk had shown statistically significant results in the subgroup analyses and thus were considered potential TEMs. These results should be interpreted with caution however, as the sample size was small for the majority of subgroups. No potential TEMs were identified for CR and CIR from the RATIFY literature (10, 86) as RATIFY *FLT3 ITD+* subgroup analyses were reported for OS only.

Quantitative assessment for TEMs in QuANTUM-First

While only aggregate data is available for RATIFY, IPD from QuANTUM-First was leveraged to conduct interaction analyses to assess the potential treatment-modifying effect of baseline characteristics. A prognostic variable test was completed to identify any baseline characteristics which may influence the outcomes of interest and a univariate regression analysis was then conducted utilising QuANTUM-First IPD to identify TEMs (i.e. characteristics affecting the treatment effect of quizartinib added to chemotherapy vs. chemotherapy alone) by introducing interaction terms of baseline characteristics with treatment in a regression model. Variables showing statistically significant association with treatment at the 75% significance level ($p \leq 0.25$) for the effect modifier test and not containing a large number of missing values, were flagged for subsequent clinical consideration (Table 24). *FLT3-ITD*$_{low}$ vs. *FLT3-ITD*$_{high}$ status, cytogenetic risk and bone marrow blast count was identified as potential TEMs for OS in QuANTUM-First. Specifically, a better treatment effect was exhibited in patients with *FLT3-ITD*$_{high}$ risk compared to those with *FLT3-ITD*$_{low}$ risk. A better treatment effect was also demonstrated in patients with a higher level of bone marrow blasts. Similar trends were demonstrated in patients with intermediate, adverse and unknown cytogenetic risk compared to those with low cytogenetic risk.

Table 24. Interaction analysis in QuANTUM-First on covariate association with OS and treatment effect modifying status

Variable		Prognostic variable test		Effect modifier test	
		HR independent of treatment	p-value for association with OS	HR for interaction with treatment	p-value interaction with treatment
Age		[redacted]	[redacted]	[redacted]	[redacted]
Sex, male		[redacted]	[redacted]	[redacted]	[redacted]
Race, White		[redacted]	[redacted]	[redacted]	[redacted]
FLT3-ITD$_{low}$ (0.05-0.7)		[redacted]	[redacted]	[redacted]	[redacted]
Cytogenetic risk	Intermediate	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse	[redacted]	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count		[redacted]	[redacted]	[redacted]	[redacted]
ANC		[redacted]	[redacted]	[redacted]	[redacted]
WBC count		NA	NA	NA	NA
Bone marrow blast count		[redacted]	[redacted]	[redacted]	[redacted]
Choice of anthracycline, daunorubicin		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ANC, absolute neutrophil count; CR, complete remission; *FLT3*, FMS-like tyrosine kinase 3; HR, hazard ratio; *ITD*, internal tandem duplication; NA, not applicable; OS, overall survival; WBC, white blood cell.
Notes: Analysis results are shown for the QuANTUM-First ITT population.

Expert consultation

In line with TSD 18 (83), three clinical experts were consulted to determine whether all relevant TEMs had been identified and to rank them according to importance. Clinicians indicated that the TEMs identified from the literature and the interaction analysis of QuANTUM-First data were plausible. From a clinical perspective, age, sex, *FLT3* mutation status, platelet count, *NPM1* mutation status and bone marrow blasts were considered TEMs for the outcomes of interest. Bone marrow blasts scored relatively low on the importance scale and thus it was not used as a TEM in the MAIC which was limited by the estimated sample size (ESS) (Table 25). Cytogenetic risk, WBC count, absolute neutrophil count (ANC), race and geographical region of patients were flagged as potential TEMs, with the former two considered most impactful. However, due to an absence of comparable data it was not possible to re-weight the population of QuANTUM-First and the *FLT3-ITD*+ population of RATIFY according to these TEMs.

Table 25. Overview of TEM variables by derivation technique and inclusion in base case analysis

TEM	Method for identification	Considered for base case
Platelet count	Expert consultation	Yes
Sex	Expert consultation	Yes
Age	Literature review, expert consultation	Yes
NPM1 mutation status	Literature review, interaction analysis, expert consultation	Yes
FLT3-ITD allelic ratio	Interaction analysis, expert consultation	Yes[a]
Bone marrow blasts[b]	Interaction analysis, expert consultation (low on importance scale)	No (included in scenario analysis)
Not analysed		
Cytogenetic risk[c]	Interaction analysis, expert consultation	No
WBC count[c]	Expert consultation	No
ANC[c]	Expert consultation	No
Geographical region[c]	Expert consultation	No
Race[c]	Expert consultation (low on importance scale)	No

Abbreviations: ANC, absolute neutrophil count; ELN, European LeukemiaNet; *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; NA, not applicable; NR, not reported; *NPM1*, nucleophosmin 1; TEM, treatment effect modifier; WBC, white blood cell.
Notes: a. this TEM was later excluded from the base case as it resulted in an ESS that was less than 50% of the original sample size. It was included as a TEM in the scenario analysis b. These were not included as they were judged to be low in terms of importance during expert consultation. c. Expert consultation/interaction analysis identified these as TEMs. However, they were not reported in the Rucker et al. publication (84) and thus matching could not be performed on these variables.

B.2.8.4 Methods

MAIC methodology

A MAIC is a population-adjusted technique and was used to mitigate the impact of between study heterogeneity. A MAIC adjusts for cross-study differences in clinically relevant TEMs and recalculates the efficacy of the treatment (quizartinib), assuming the drug is used in patient populations similar to those of the respective comparator trial (RATIFY).

The re-weighting methodology statistically constructs trial patient populations that are similar so that the outcomes from the trials can be meaningfully compared. All TEMs (both those that were balanced and those that were imbalanced between the studies) were considered in the re-weighting model, while variables exhibiting a purely prognostic property were disregarded to avoid inflating standard error due to over-matching, as per NICE advice for anchored MAICs (83).

Published summary statistics for OS, CR and CIR were retrieved from the Rücker et al. publication on *ITD* (+) patients in the RATIFY trial whilst IPD from QuANTUM-First was used.

The coding of the MAIC was performed according to Appendix D of NICE DSU TSD 18 (83). Adjustment according to identified TEMs was done through inverse propensity score weighting. Patients within QuANTUM-First who were more likely to be among the target aggregate population of RATIFY *FLT3-ITD*+ patients given their characteristics were assigned higher weights in the analysis and vice versa. To achieve this, inverse odds were estimated for each QuANTUM-First patient, representing the probability of the patient being part of RATIFY's trial *ITD* (+) population. These odds were used as weights to create the matched population. Propensity score weights were estimated using logistic regression:

$$log(w_{it}) = a_0 + a_1^{\mathrm{T}} X_{it}^{\mathrm{EM}}$$

Where X_{it}^{EM} is the effect modifier covariate vector for the *i*-th individual in QuANTUM-First study and w_{it} is the weight of the *i*-th individual. As IPD was not available for RATIFY, the weights could not be estimated using standard logistic regression methods. Instead, the method of moments approach was used to estimate $\hat{a}_1$ so that the weights balance the mean covariate values between the populations of MAIC-reweighted QuANTUM-First and the RATIFY ITT and *ITD* (+) populations.

The loss of statistical information in the reweighted trial data is reflected in the ESS being lower than the initial sample size of the QuANTUM-First trial. The ESS was estimated as:

$$\mathrm{ESS} = \frac{\left(\sum_{\mathrm{i}=1}^{\mathrm{N}} \widehat{\mathrm{w}}_{\mathrm{i}}\right)^2}{\sum_{\mathrm{i}=1}^{\mathrm{N}} \widehat{\mathrm{w}}_{\mathrm{i}}{}^2}$$

ESS is defined as 'the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate' (83). A small ESS is indicative of highly variable weights due to a lack of population overlap and as such, the estimates may be unstable. As all TEMs, either imbalanced or balanced, should be adjusted for in a MAIC, the model in which as many covariates

as possible were included was used, while maintaining an ESS. Matching variables for the MAIC were included via stepwise forward inclusion (i.e. the highest-ranking TEM was included in the first model and each additional TEM was then included according to rank if the ESS with all the matching variables included remained above 50% of the original sample size). For the MAIC base case, TEMs were added until the ESS of the adjusted QuANTUM-First population (effectively a 'RATIFY-like' population) reached 50% of the initial sample size. Scenario analyses including the remaining TEMs (allowing ESS to fall below 50%) were also conducted.

To diagnose population overlap, the distribution of weights themselves was examined. Rescaled weights were calculated using the following formula and presented in histograms:

$$\widehat{\omega}_i = \frac{\widehat{w}_i}{\sum_{i=1}^{N} \widehat{w}_i} \times N$$

where N is the number of subjects in QuANTUM-First. Rescaled weights > 1 indicate that a patient carries more weight in the reweighted pseudo-population than the original trial sample, while a rescaled weight <1 means that an individual carries less weight in the reweighted population than the original data.

Relative treatment effects for outcomes (OS, CR and CIR) were estimated using log HR and odds ratios (OR) and their standard errors. The choice of log HR/OR – the linear predictor – scale follows the NICE MAIC recommendations (83). The assumed linearity, additivity of treatment effects and treatment effect modification on this scale is required for estimating the relative treatment effect of quizartinib and midostaurin in the target (AC) population:

$$g(\hat{\Delta}_{BC(AC)}) = g(\hat{\Delta}_{AC(AC)}) - g(\hat{\Delta}_{AB(AC)})$$

where A is placebo, B is quizartinib, C is midostaurin, g is a link function – log(.) in this case, $\hat{\Delta}_{BC(AC)}$ is the (indirect) relative treatment effect (HR) of quizartinib vs. midostaurin in the target AC population, $\hat{\Delta}_{AC(AC)}$ is the treatment effect (HR) of placebo vs. midostaurin in the target AC population and $\hat{\Delta}_{AB(AC)}$ is the treatment effect (HR) of

placebo vs. quizartinib - estimated using MAIC reweighting and applying the weighted Cox proportional hazards (PH) model - in the target AC population (10).

The relative treatment effects based on weighted HRs/ORs were reported. In order to calculate the corresponding standard errors, a robust sandwich variance estimation was used. An alternative method was used to calculate the 95% CI and standard error based on bootstrap resampling (with replacement). The bootstrap was performed using 1,000 bootstrap samples, and the 95% CI was estimated using the 2.5th and 97.5th percentiles of the bootstrap distributions.

To increase the robustness of the results, scenario analyses were conducted. Each of these analyses adds in an additional TEM which was originally considered in the base case MAIC but was later ruled out due to the ESS dropping below 50% on addition:

- Analysis of OS, CR, and CIR using all the matching variables considered for the base case (i.e. All TEMs used in the base case plus *FLT3-ITD* allelic ratio [>0.5]).
- Analysis of OS, CR, and CIR using baseline bone marrow blasts in addition to the matching variables used in the base case (i.e. All TEMs used in the base case plus baseline bone marrow blasts)

Naïve comparison

In the naïve comparisons, the patient populations of QuANTUM-First and RATIFY *FLT3-ITD* were directly compared without any population re-weighting, using the same equation as in the MAIC to estimate the relative treatment effect between quizartinib and midostaurin. The results of the naïve comparisons acted as a control to assess whether performing MAICs improved comparability of the treatment effects among quizartinib, midostaurin and placebo in comparison with the naïve unadjusted ITCs.

B.2.8.5 Results of the MAIC

Anchored comparison using QuANTUM-First

Two of the baseline characteristics identified as TEMs were similar across the unadjusted studies i.e. sex and age (Table 26). However, platelet counts, *NPM1* mutation status and *FLT3-ITD* allelic ratio at baseline were found to be imbalanced. Platelet count and *NPM1* mutations status were used as TEMs in the re-weighting

process, however, the data was not adjusted according to *FLT3-ITD* allelic ratio or Bone Marrow blasts as the ESS fell far below 50% of the actual sample size of the QuANTUM-First trial population. The QuANTUM-First population was thus re-weighted for four of the TEMs: platelet count, sex, age and *NPM1* mutation status. The ESS was [redacted], accounting for [redacted] of the patients aged under 60 years from QuANTUM-First. The adjusted QuANTUM-First population showed improved alignment of baseline characteristics with RATIFY for the TEMs that were accounted for in the re-weighting process (platelet count, sex, age and *NPM1* mutation status). Although the mean platelet counts were aligned after re-weighting, differences remained between the median platelet counts, indicating that not all imbalances were resolved between the populations and that residual bias may remain.

Table 26. Summary of patient characteristics included in the MAIC comparing quizartinib (QuANTUM-First ITT population up to age 60) and midostaurin (RATIFY *FLT3-ITD*+ population)

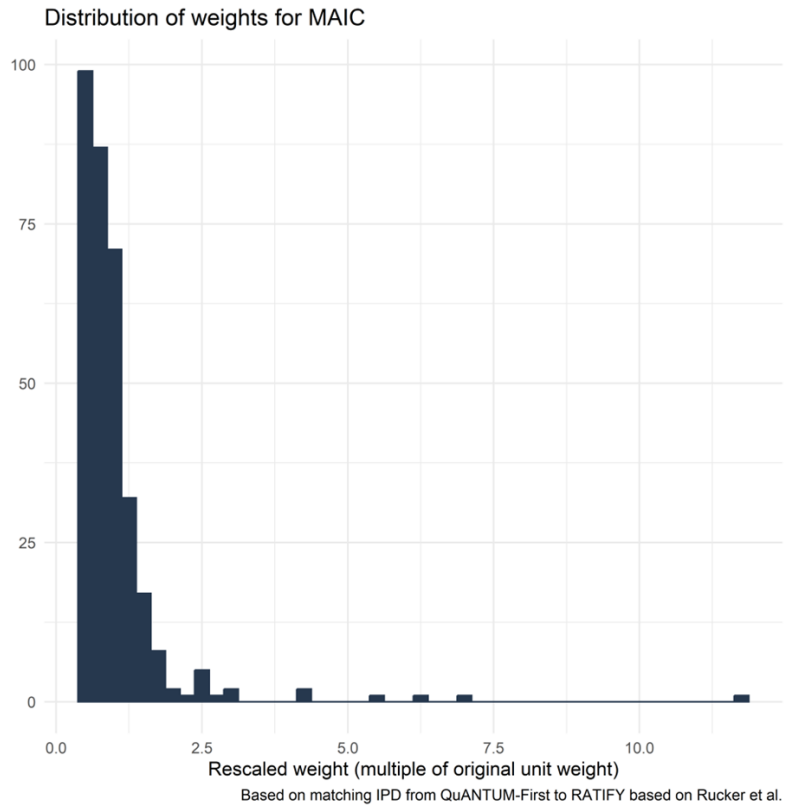
Matching variable	QuANTUM-First unadjusted ([redacted])	QuANTUM-First Adjusted (ESS=[redacted])	RATIFY *FLT3-ITD* population (N=452)
TEMs (Base case)			
Platelet count x 10^9/L, mean	[redacted]	[redacted]	50[a]
Platelet count, x 10^9/l, median (min, max)	[redacted]	[redacted]	50 (2, 461)
Sex, male, n (%)	[redacted]	[redacted]	206 (45.6)
Age, mean	[redacted]	[redacted]	47[a]
Age, median (min, max)	[redacted]	[redacted]	47 (18, 60)
NPM1 mutation status, positive, n (%)	[redacted]	[redacted]	203 (56.7)
TEMs excluded due to the resulting ESS falling below 50% of the original sample size			
FLT3-ITD allelic ratio, >0.5, n (%)	[redacted]	[redacted]	290 (64.3)

Abbreviations: ESS, estimated sample size; *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; ITT, intent-to-treat; MAIC, matching adjusted indirect comparison; *NPM1*, nucleophosmin 1; TEM, treatment effect modifier.
Reference: Rücker et al., 2021 (84), Daiichi Sankyo, 2023 (85)
Notes: a. Given only the median platelet count, the median age and median bone marrow blast count were available from *FLT3-ITD*+ patient population of RATIFY but the matching approach utilises the mean, it was assumed that median and mean were equal. Re-weighting was conducted on the assumed means, but the medians are presented here for comparison.

The distribution of the resulting weights was centred around one, as shown in Figure 16. Four outliers with weights above five were identified with a maximum weight of [redacted]. An investigation into the patients with high weights indicated that being highly

weighted was correlated with having a high platelet count. It is justified that patients with high platelet counts would be more highly weighted in the matching process given the higher median and maximum platelet count in RATIFY compared with the <60 years QuANTUM-First trial population.

Figure 16. Propensity score weights for QuANTUM-First



Abbreviations: IPD, individual patient data; MAIC, matching adjusted indirect comparison.
Reference: Daiichi Sankyo, 2023 (85)

Overall survival

Prior to matching, both quizartinib and midostaurin demonstrated favourable efficacy vs. placebo, as indicated by the OS HRs in QuANTUM-First and RATIFY respectively (Table 27). A naïve comparison indicated a HR of [redacted] (95% CI: [redacted] to [redacted]) between quizartinib and midostaurin.

Re-weighting shifted the quizartinib and placebo curves of QuANTUM-First upwards (Figure 17). The median OS before matching in QuANTUM-First was not reached in the quizartinib arm and was [redacted] months in the placebo (95% CI: [redacted] to [redacted]) arm. Post matching, again the median OS for the quizartinib arm was not reached while the placebo arm had a median OS of [redacted] (95% CI: [redacted] to [redacted]) months.

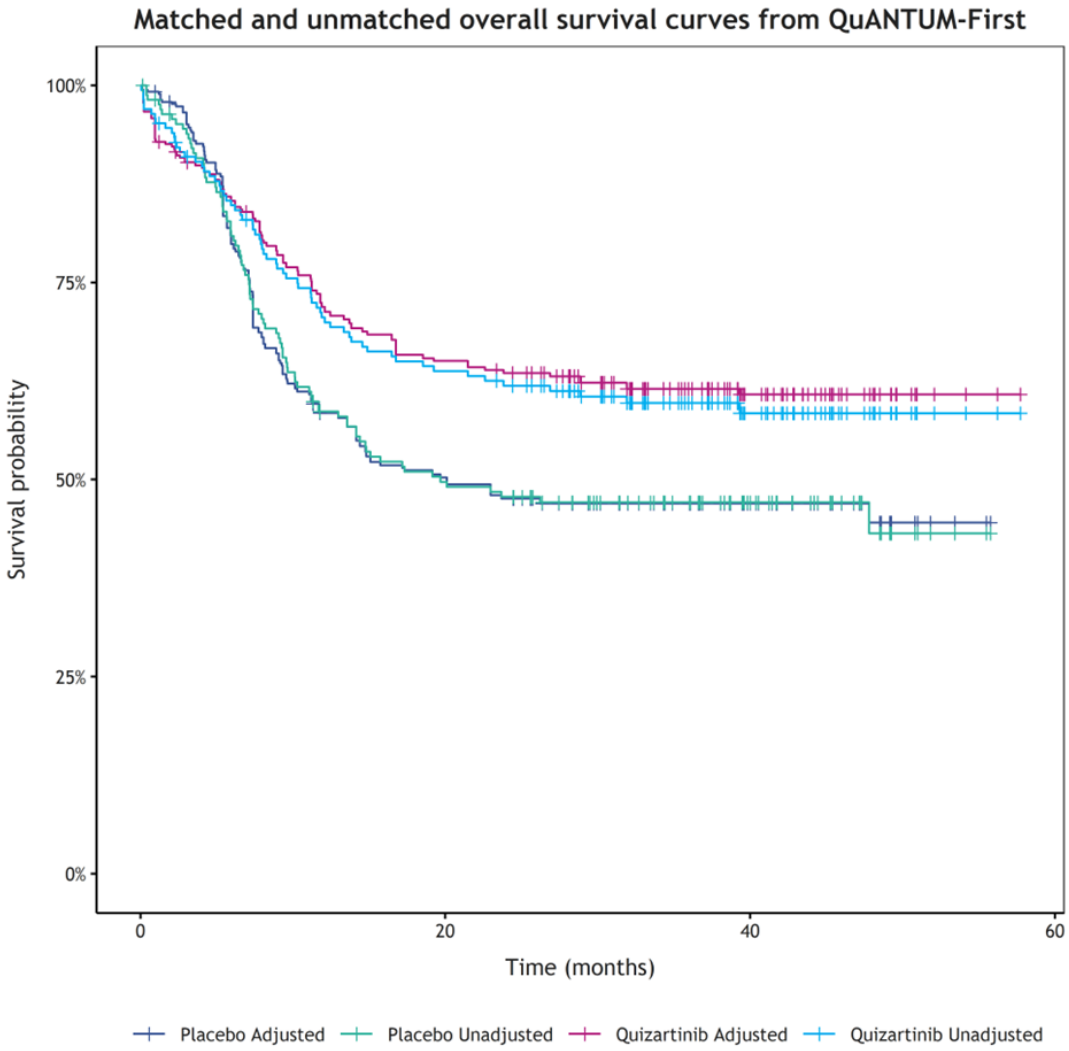
The MAIC of OS between quizartinib and midostaurin based on the adjusted QuANTUM-First population and RATIFY *FLT3-ITD* populations showed numerically favourable outcomes with quizartinib as compared to midostaurin (HR: [redacted]; 95% CI: [redacted] to [redacted]).

Table 27. Overall survival – quizartinib (QuANTUM-First ITT population aged below 60) and midostaurin (RATIFY *FLT3-ITD*+ population)

Method	Comparison	HR (95% CI)
QuANTUM-First unadjusted[a]	Quizartinib vs. placebo	0.68 (0.50, 0.94)
QuANTUM-First weighted[b]	Quizartinib vs. placebo	0.65 (0.42, 1.00)
RATIFY	Midostaurin vs. placebo	0.79 (0.59, 1.06)
Naïve	Quizartinib vs. midostaurin	0.87 (0.56, 1.34)
MAIC[c]	Quizartinib vs. midostaurin	0.82 (0.48, 1.39)

Abbreviations: CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; HR, hazard ratio; *ITD*, internal tandem duplication; ITT, intent-to-treat; MAIC, matching adjusted indirect comparison.
References: Rücker et al., 2021 (84); Daiichi Sankyo, 2023 (85)
Notes: a. HR and 95% CI from stratified Cox PH model. b. HR from weighted Cox PH model. CI was computed using the robust sandwich variance estimation. c. CI was computed using the robust sandwich variance estimation.

Figure 17. Matched and unmatched overall survival curves from QuANTUM-First



Reference: Daiichi Sankyo, 2023 (85)

Complete remission

Prior to matching, both quizartinib and midostaurin demonstrated favourable efficacy vs. placebo, as measured by the CR ORs from QuANTUM-First and RATIFY respectively (Table 28). A naïve comparison indicated an OR of [redacted] (95% CI: [redacted] to [redacted]) between quizartinib and midostaurin. The MAIC of CR between quizartinib and midostaurin based on the adjusted QuANTUM-First population and RATIFY *FLT3-ITD* populations showed numerically less favourable outcomes with quizartinib as compared to midostaurin (OR: [redacted]; 95% CI: [redacted] to [redacted]). However, this result was not statistically significant.

Table 28. Complete remission – quizartinib (QuANTUM-First ITT population aged below 60) and midostaurin (RATIFY *FLT3-ITD*+ population)

Method	Comparison	OR (95% CI)
QuANTUM-First unadjusted	Quizartinib vs. placebo	1.04 (0.67, 1.60)
QuANTUM-First weighted	Quizartinib vs. placebo	1.14 (0.62, 2.12)
RATIFY	Midostaurin vs. placebo	1.25 (0.79, 1.99)
Naïve	Quizartinib vs. midostaurin	0.83 (0.44, 1.56)
MAIC	Quizartinib vs. midostaurin	0.92 (0.42, 1.97)

Abbreviations: CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; ITT, intent-to-treat; MAIC, matching adjusted indirect comparison; OR, odds ratio.
References: Rücker et al., 2021 (84); Daiichi Sankyo, 2023 (85)

Cumulative incidence of relapse

Prior to matching, both quizartinib and midostaurin demonstrated favourable efficacy vs. placebo, as indicated by the CIR HRs (Table 29) from QuANTUM-First and RATIFY respectively. A naïve comparison of the relative efficacy of quizartinib and midostaurin revealed a HR of [redacted] (95% CI: [redacted] to [redacted]).

Re-weighting shifted the CIR quizartinib curve of the QuANTUM-First trial downwards and the placebo curve of the same trial upwards, improving the relative effectiveness of quizartinib vs. placebo (Figure 18). The upwards shift of the placebo curve of QuANTUM-First was pronounced and featured two identifiable moments of relapse (around three months and six months), which were caused by placebo patients with a higher weight experiencing relapse events.

The HR of quizartinib vs. placebo was [redacted] (95% CI: [redacted] to [redacted]) before matching and [redacted] (95% CI: [redacted] to [redacted]) after matching. The MAIC of CIR between quizartinib and

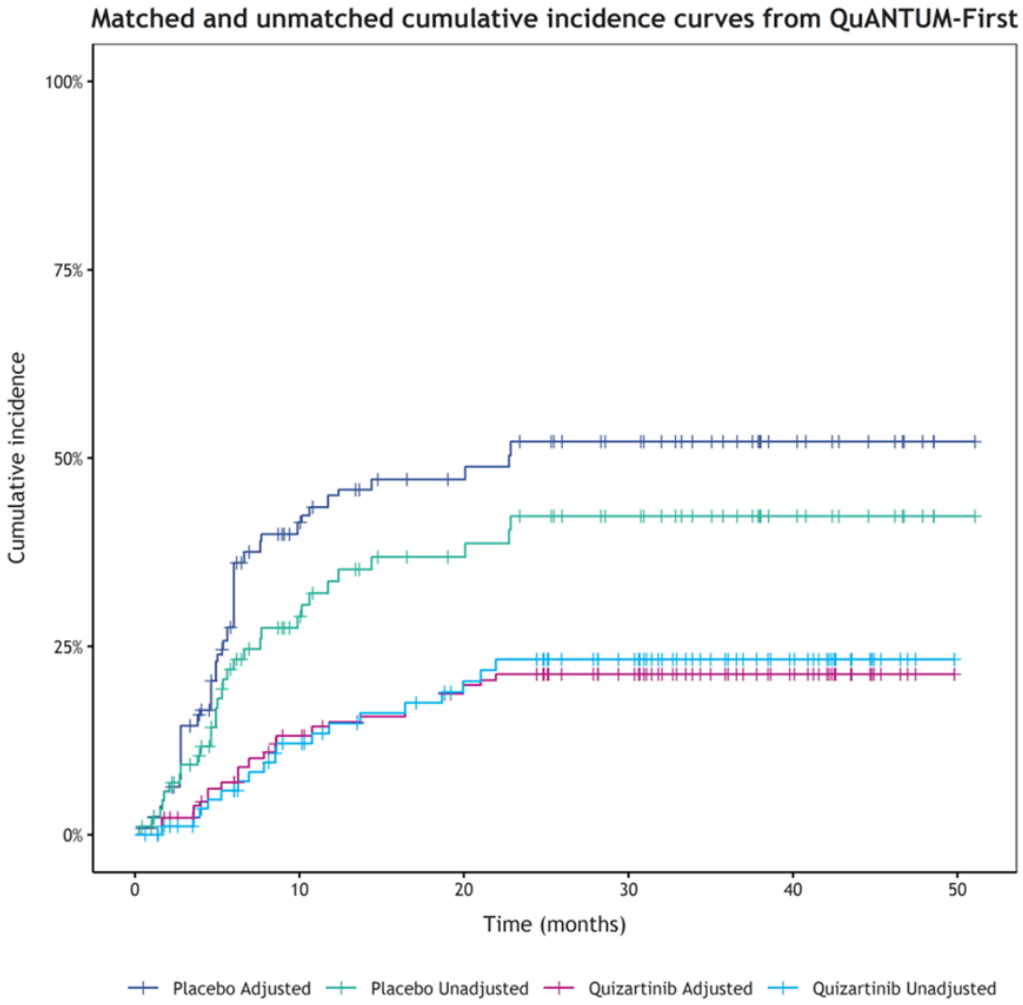
midostaurin favours quizartinib with a HR of [redacted] (95% CI: [redacted] to [redacted]), which compares to the naive HR of 0.61 (95% CI: 0.31, 1.19).

Table 29. Cumulative incidence of relapse – quizartinib (Ajusted QuANTUM-First population) and midostaurin (RATIFY *FLT3-ITD*+ population)

Method	Comparison	HR (95% CI)
QuANTUM-First unadjusted[a]	Quizartinib vs. placebo	0.49 (0.28, 0.86)
QuANTUM-First adjusted[b]	Quizartinib vs. placebo	0.34 (0.17, 0.66)
RATIFY	Midostaurin vs. placebo	0.80 (0.56, 1.15)
Naïve	Quizartinib vs. midostaurin	0.61 (0.31, 1.19)
MAIC[c]	Quizartinib vs. midostaurin	0.42 (0.20, 0.91)

Abbreviations: CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; HR, hazard ratio; *ITD*, internal tandem duplication; ITT, intent-to-treat; MAIC, matching adjusted indirect comparison.
References: Rücker et al., 2021 (84); Daiichi Sankyo, 2023 (85)

Figure 18. Matched and unmatched cumulative incidence of relapse curves from QuANTUM-First



Reference: Daiichi Sankyo, 2023 (85)

Scenario analyses

A description of the scenario analyses conducted is presented Table 30.

Table 30. Description of scenario analyses

Scenario	Description	TEMs used
Scenario 1	All TEMs used in the base case and subtype of *FLT3-ITD* allelic ratio (>0.5)	Platelet count, sex, age, *NPM1* mutation status, subtype of *FLT3-ITD* allelic ratio (>0.5)
Scenario 2	All TEMs used in base case and baseline bone marrow blasts	Platelet count, sex, age, *NPM1* mutation status, baseline bone marrow blasts

Abbreviations: *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; *NPM1*, nucleophosmin 1; TEM, treatment effect modifier.

Scenario 1: Overall survival using a different set of TEMs

Baseline characteristics before and after matching in this scenario analysis for QuANTUM-First and RATIFY are provided in Table 31. Several characteristics identified as TEMs, or baseline characteristics identified as potential TEMs were similar across the unadjusted studies, such as sex and age. However, platelet counts at baseline, *NPM1* mutation status and *FLT3-ITD* allelic ratio were found to be imbalanced. Platelet count, *NPM1* mutations status, age, sex, and *FLT3-ITD* allelic ratio were used as TEMs for matching. The resulting matched QuANTUM-First population had an ESS of 162.99, representing a reduction of the sample size by 50.8%.

Table 31. Summary of patient characteristics included in the MAIC – quizartinib adjusted QuANTUM-First population up to age 60) and midostaurin (RATIFY *FLT3-ITD* (+) population) – Scenario 1

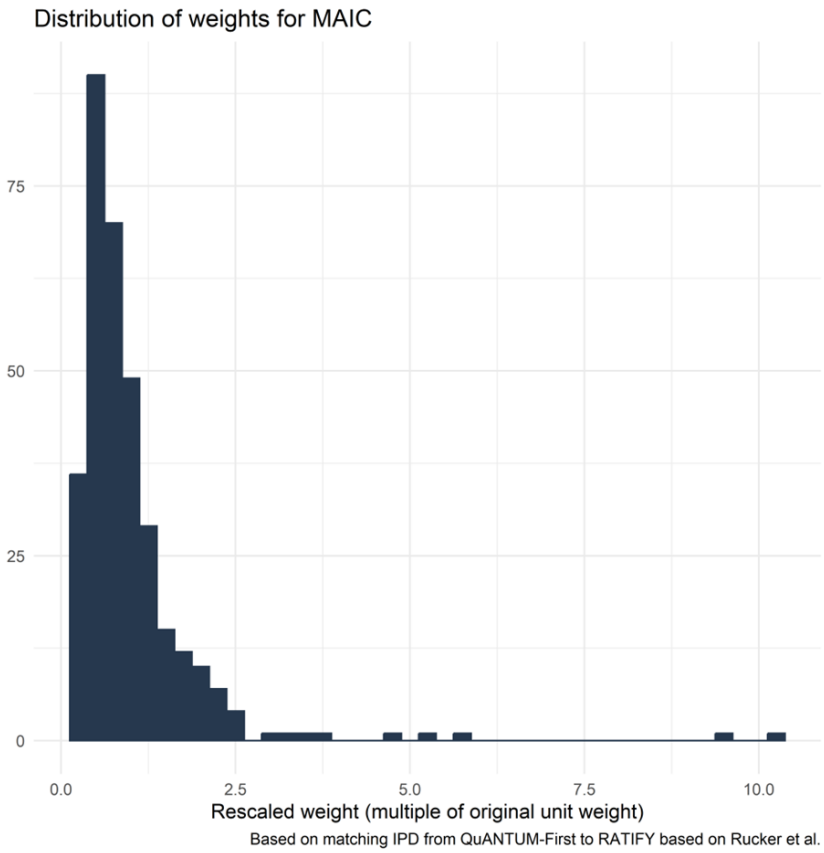
Treatment effect modifiers used for matching: Scenario 1		QuANTUM-First unadjusted N = 331	QuANTUM-First adjusted ESS = 162.99	RATIFY *ITD* (+) population N = 452
TEMs that were also used in the base case analysis	Platelet count, x 10^9/L, mean[a]	[redacted]	[redacted]	50
	Platelet count, x 10^9/L, median (min, max)	[redacted]	[redacted]	50 (2, 461)
	Sex, male, n (%)	[redacted]	[redacted]	206 (45.6%)
	Age, mean[a]	[redacted]	[redacted]	47
	Age, median (min, max)	[redacted]	[redacted]	47 (18-60)

Treatment effect modifiers used for matching: Scenario 1		QuANTUM-First unadjusted N = 331	QuANTUM-First adjusted ESS = 162.99	RATIFY *ITD* (+) population N = 452
	NPM1 mutation status, positive, n (%)	[redacted]	[redacted]	203 (56.7%)
TEMs added in scenario 1	Subtype of *FLT3-ITD* allelic ratio, >0.5, n (%)	[redacted]	[redacted]	290 (64.3%)

Abbreviations: ESS, effective sample size of the weighted analysis set; *FLT3*, FMS-like tyrosine kinase 3; *ITD*, internal tandem duplication; MAIC, matching adjusted indirect comparison; max, maximum; min, minimum; *NPM1*, nucleophosmin 1; TEM, treatment effect modifier.
References: Stone et al. 2017 (10); Daiichi Sankyo, 2023 (85)
Notes: a. Given only the median was available from RATIFY, but the matching approach utilises the mean, it was assumed that median and mean were equal. Matching was conducted on the assumed mean from RATIFY, but medians are presented for comparison.

The majority of the distribution of the resulting weights were centred around one, as shown in Figure 19. Four outliers with weights above five were identified in the matching between QuANTUM-First and RATIFY, with a maximum weight identified of 10.23. Investigation of patients with high weights indicated that they correlated with those with high platelet counts. Given the higher median and maximum platelet count observed in RATIFY, patients with high platelet counts were comparatively under-represented in the under 60 QuANTUM-First trial population and thus received higher weights during matching.

Figure 19. Propensity score weights for QuANTUM-First population matched with RATIFY *FLT3-ITD* (+) population – Scenario 1



Abbreviations: IPD, individual patient data; MAIC, matching adjusted indirect comparison.
Reference: Daiichi Sankyo, 2023 (85)

Scenario 2: Base case with baseline bone marrow blasts as an additional TEM

Baseline characteristics before and after matching for QuANTUM-First and RATIFY are provided in Table 32. Several characteristics identified as TEMs, or baseline characteristics identified as potential TEMs were similar across the unadjusted studies, such as sex and age. However, platelet counts at baseline, *NPM1* mutation status, *FLT3-ITD* allelic ratio, and bone marrow blasts at baseline were found to be imbalanced. Platelet count, *NPM1* mutations status, age, sex, and bone marrow blasts were used as TEMs for matching. The resulting matched QuANTUM-First population had an ESS of 138.38, representing a reduction of the sample size by 58.2%.

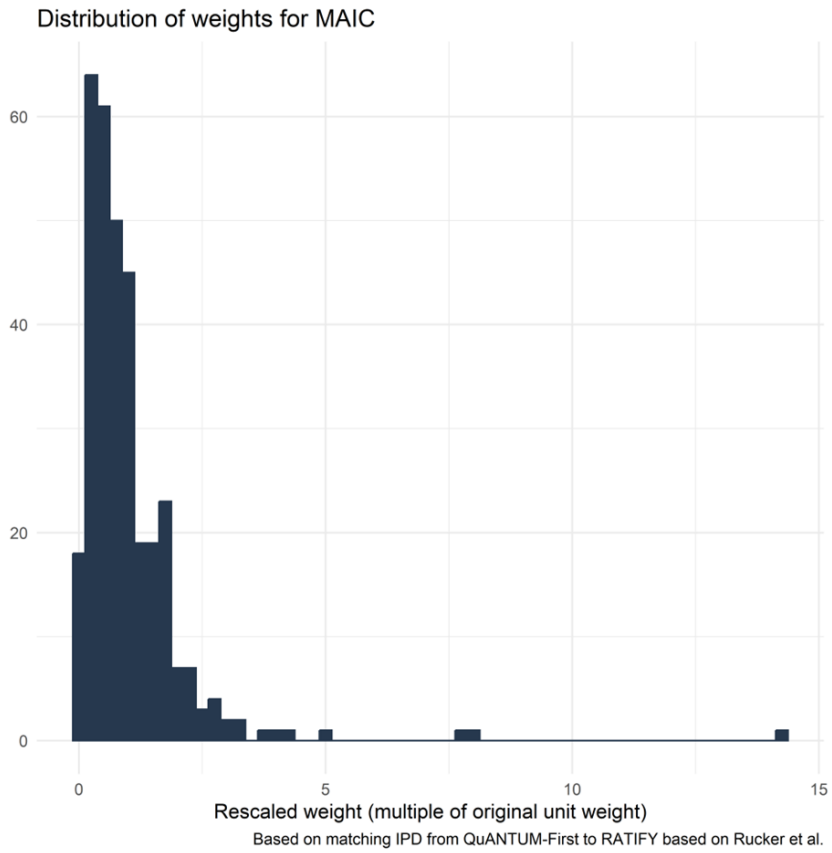
Table 32. Summary of patient characteristics included in the MAIC – quizartinib (QuANTUM-First population up to age 60) and midostaurin (RATIFY *FLT3-ITD* (+) population) – Scenario 2

Treatment effect modifiers used for matching: Scenario 2		QuANTUM-First unadjusted N = 331	QuANTUM-First adjusted ESS = 138.38	RATIFY *ITD* (+) population N = 452[84]
TEMs that were also used in the base case analysis	Platelet count, x 10^9/l, mean[a]	[redacted]	[redacted]	50
	Platelet count, x 10^9/l, median (min, max)	[redacted]	[redacted]	50 (2, 461)
	Sex, male, n (%)	[redacted]	[redacted]	206 (45.6%)
	Age mean[a]	[redacted]	[redacted]	47
	Age median (min, max)	[redacted]	[redacted]	47 (18-60)
	NPM1 mutation status, positive, n (%)	[redacted]	[redacted]	203 (56.7%)
TEMs added in scenario 2	Bone marrow blasts mean[a]	[redacted]	[redacted]	79
	Bone marrow blasts median (min, max)	[redacted]	[redacted]	79 (3, 100)

Abbreviations: ESS, effective sample size; MAIC, matching adjusted indirect comparison; max, maximum; min, minimum; *NPM1*, nucleophosmin 1; TEM, treatment effect modifier.
References: Daiichi Sankyo, 2023 (85)
Notes: a. Given only the median was available from RATIFY, but the matching approach utilises the mean, it was assumed that median and mean were equal. Matching was conducted on the assumed mean from RATIFY, but medians are presented for comparison.

The majority of the distribution of the resulting weights were centred around one, as shown in Figure 20. Four outliers with weights above five were identified in the matching between QuANTUM-First and RATIFY, with a maximum weight of 13.62. An investigation of patients with high weights indicated that high weights correlated with those with high platelet counts. Given the higher median and maximum platelet count observed in RATIFY, patients with high platelet counts were comparatively under-represented in the under 60s QuANTUM-First trial population and thus received higher weights during matching.

Figure 20. Propensity score weights for QuANTUM-First population matched with RATIFY *FLT3-ITD* (+) population – Scenario 2



Abbreviations: IPD, individual patient data; MAIC, matching adjusted indirect comparison.
Reference: Daiichi Sankyo, 2023 (85)

Scenario analyses results summary

The results of the scenario analyses (Table 33) show that there is largely consistency in the MAIC results between the base case and the scenarios. The MAIC results from scenarios 1 and 2 found an improved benefit of quizartinib over midostaurin in CIR as compared to the base case. As with the base case the scenario analyses for OS largely showed a benefit in favour of quizartinib that was not statistically significant. For CR, the direction of benefit varied across the base case and the scenario analyses, however, neither the base case nor the scenario analyses showed a statistically significant result for this outcome.

Table 33. Scenario analysis results

		OS HR (95% CI)[a]			CR OR (95% CI)[b]			CIR HR (95% CI)[c]		
Method	**Comparison**	**Basecase**	**Scenario 1**	**Scenario 2**	**Basecase**	**Scenario 1**	**Scenario 2**	**Basecase**	**Scenario 1**	**Scenario 2**
QuANTUM-First unadjusted	Quiz vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QuANTUM-First weighted	Quiz vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RATIFY	Mido vs PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Naïve	Quiz vs mido	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAIC	Quiz vs mido	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; HR, hazard ratio; MAIC, matching adjusted indirect comparison; mido, midostaurin; OR, odds ratio; OS, overall survival; PBO, placebo; quiz, quizartinib.
References: Daiichi Sankyo, 2023 (85)
Notes: a. The HR and 95% CI for the QuANTUM-First unadjusted method were from the stratified Cox PH model. The HR for the QuANTUM-First weighted method were from a weighted Cox PH model. The CI was computed using the robust sandwich variance estimation. The HR and 95% CI for the analysis of RATIFY are from Cox PH model based on Stone et al. The MAIC CI was computed using the robust sandwich variance estimation.
b. The OR for the QuANTUM-First unadjusted method was based on weighted logistic regression with binomial link. The CI was computed using the robust sandwich variance estimation. The RATIFY analysis was based on analysis by Stone et al.(10). It was computed using the robust sandwich variance estimation.
c. The HR and 95% CI for the QuANTUM-First unadjusted method were from Fine-Gray competing risk model. The HR for the QuANTUM-First weighted method were from weighted Fine-Gray competing risk model. The CI was computed using the robust sandwich variance estimation. The HR and 95% CI for the RATIFY data were from Fine-Gray competing risk model based on digitised IPD from Stone et al.(10). The MAIC CI was computed using the robust sandwich variance estimation.

B.2.8.6 Conclusions

The OS HR from the MAIC numerically favoured quizartinib (HR: [redacted]; 95% CI: [redacted] to [redacted]). The CIR HR from the MAIC also favoured quizartinib and was statistically significant (HR: [redacted]; 95% CI: [redacted] to [redacted]). The CR OR from the MAIC numerically favoured midostaurin, however, this was not statistically significant (OR: [redacted]; 95% CI: [redacted] to [redacted]) in this nominal analysis and the direction of benefit varied in the scenarios tested.

Results from naïve comparisons between quizartinib and midostaurin generally aligned with the results of the MAICs. Matching shifted the relative effectiveness outcomes for all outcomes in favour of quizartinib, which was in line with what clinical experts had expected after the QuANTUM-First population was matched to the RATIFY population, and generated a slightly improved OS outcome in patients that received quizartinib. While matching improved the CR OR for quizartinib, the results remained slightly favourable for midostaurin. Improved CR was in line with expectations given CR might be achieved faster in a healthier population like that of RATIFY. Weighting had a positive effect on the CIR HR for QuANTUM-First. Expert opinion stated that expectations for relapse after CR were less clear, given randomisation between the treatment arms no longer applied.

The results of the MAIC in the scenario analyses were in line with the base case results for OS and CIR highlighting the robustness of the MAIC under different assumptions, there was a variation in terms of direction of benefit for the CR outcome but this was not statistically significant. The HRs for OS were largely similar in the scenario analyses and the base case, while in the scenario analyses for CIR improved HRs were observed which favoured quizartinib over midostaurin to a greater degree than in the base case (HR in the scenario analysis 1: [redacted]; 95% CI: [redacted] to [redacted]; HR in scenario analysis 2: [redacted]; 95% CI: [redacted] to [redacted]; HR in the base case: [redacted]; 95% CI: [redacted] to [redacted]).

Considering that the remaining imbalance in platelet count was not resolved by reweighting, there is a potential for bias in the results of this MAIC. The adjusted QuANTUM-First population presented with a median platelet count of [redacted]/L, while the RATIFY *FLT3-ITD* population exhibited a median platelet count of 50×10^9/L. The

direction of bias resulting from the difference in median platelet count across the two populations is unclear, as the available evidence presents inconsistent results regarding the effects of platelet count on OS in AML patients. One study found that lower platelet counts (≤40 × 10^9/L) at diagnosis of AML was associated with an improved 5-year OS rate than those with a higher platelet count (>40 × 10^9/L) (87), while another study found that AML patients with medium pre-treatment platelet count (50-120 × 10^9/L) at diagnosis had longer OS than those with low (<50 × 10^9/L) or high platelet counts (>120 × 10^9/L) (88). This may have affected the relative treatment effect between quizartinib and midostaurin. Adjustment of the population for platelet count resulted in higher weights being assigned to four patients, allowing for those patients to potentially influence the matched outcomes significantly.

The MAIC was conducted in line with NICE DSU TSD 18 (83) and with the support of clinical expert opinion on the selection of TEMs. It should be noted that there are some general limitations to the re-weighting methodology. Firstly, potential bias may be present from the remaining heterogeneity stemming from parameters that could not be compared between the trial populations due to limitations in reported data. Specifically, HSCT rate was not accounted for in this MAIC as it is not a baseline characteristic. However, use of transplantation was considerably higher in RATIFY with 59% of the midostaurin group and 55% of the placebo group, respectively (10). In QuANTUM-First, [redacted] of patients in quizartinib arm and [redacted] in placebo arm received a transplant (73). Higher use of transplantation may have affected OS and duration of CIR by resulting in more durable remission and survival. However, the impact of this difference between the two populations favours RATIFY outcomes, and thus absence of adjustment is expected to be conservative. Secondly, as mean values were not reported for TEMs by Rücker et al. (84) a simplifying assumption that the reported median and mean were equal was required for re-weighting. Thirdly, it was not possible to adjust for all differences in TEMs between trial populations which may have introduced bias. The re-weighting process results in the loss of statistical information due to a reduced ESS of the re-weighted population. Re-weighting on a larger number of variables yields a larger reduction in ESS. Therefore, to limit the reduction in ESS to 50%, careful selection of TEMs was necessary and it was not possible to adjust for all relevant TEMs. Fourthly, the distribution of weights was not equal, indicating that

some QuANTUM-First patients with high weights had a larger impact on the post-adjustment QuANTUM-First HR.

In summary, the MAICs conducted assessed the relative treatment effectiveness between midostaurin and quizartinib in a population matched to the RATIFY trial population. While there are some limitations, the analysis results consistently indicated that treatment with quizartinib would result in CR comparable to midostaurin, with a reduced risk in OS, and in a significantly reduced risk of relapse in patients that achieved CR.

B.2.8.7 Additional indirect treatment comparison

In addition to the MAIC analysis, a multilevel network meta-regression (ML-NMR) was also conducted. As opposed to the MAIC, which is constrained to the population of the aggregate comparator study, the ML-NMR provides flexibility to generate estimates for any specified target population.

However, the methodology of ML-NMR is based on several strong assumptions. First, the numerical integration points are derived from the marginal distribution selected for the relevant covariates. This, however, assumes a linear interpolation, which may oversimplify the data. Furthermore, in the absence of sufficient data to define treatment-specific interaction coefficients, the assumption of shared effect modifiers is employed. Additionally, an M-spline approach is employed to model the baseline hazard over time. While the M-spline model has shown a superior statistical fit compared to accelerated failure time and proportional hazards parametric models, uncertainty is introduced by fitting functional forms on time-to-event outcomes when using ML-NMR estimates. In contrast, estimating the HR directly from IPD, such as with the MAIC method, avoids this additional assumption.

Given the complexity of the ML-NMR approach, MAIC estimates are used in the CEM base case. The ML-NMR estimates were explored in a scenario analysis in cost-effectiveness analysis (see section B.3.9.3).

Detailed methodology and results of the ML-NMR were provided in the Appendix M.

B.2.9 Meta-analysis

A meta-analysis was not conducted.

B.2.10 Adverse reactions

Overall, the safety results observed in the QuANTUM-First study demonstrated that quizartinib, when administered with standard induction and consolidation chemotherapy and then as maintenance monotherapy post consolidation for up to 36 cycles, has a safety profile that is manageable with monitoring and dose modification (21).

B.2.10.1 Drug exposure

The median treatment duration for all patients who received more than one dose of study drug was 10.71 weeks for quizartinib and 9.50 weeks for placebo (21). In both treatment arms, subjects received a median of [redacted] treatment cycles (73). The median cumulative dose was [redacted] and [redacted] for patients in the quizartinib and placebo arm, respectively, and in terms of relative dose intensity, the median was [redacted] for both treatment arms (range: [redacted] with quizartinib and [redacted] with placebo). The percentages of patients experiencing at least one dose interruption and one dose reduction were higher with quizartinib than with placebo and they occurred predominantly due to AEs (Table 34) (73).

The adjusted treatment duration in each phase and the median number of cycles subjects received were [redacted] between the quizartinib and placebo arms. The median (min, max) adjusted treatment durations of quizartinib and placebo were [redacted] weeks and [redacted] weeks in induction, respectively, [redacted] weeks and [redacted] weeks, respectively, in consolidation, and [redacted] weeks and [redacted] weeks, respectively, in maintenance. In both treatment arms, the median (min, max) numbers of cycles of treatment were [redacted] cycle in induction and [redacted] cycles in consolidation. In maintenance, subjects were treated for a median of [redacted] cycles in the quizartinib arm and [redacted] cycles in the placebo arm (Table 34) (73). Further post-hoc analysis exploring drug exposure in maintenance based on protocol-specified HSCT found mean (SD) treatment duration in patients with protocol-specified HSCT was [redacted] weeks in the quizartinib arm

and [redacted] weeks in the placebo arm. Mean (SD) treatment duration in patients without protocol-specified HSCT was [redacted] weeks in the quizartinib arm and [redacted] weeks in the placebo arm.

Table 34. Summary of drug exposure, overall study period and by treatment phase (safety analysis set)

Category	Quizartinib	Placebo
Overall period	**N = 265**	**N = 268**
Treatment duration in weeks, [a] mean (SD); median (min, max)	[redacted] 10.71 (0.1, 184.1)	[redacted] 9.50 (0.4, 181.9)
Adjusted treatment duration [b] of study drug in weeks, mean (SD); median (min, max)	[redacted]	[redacted]
Number of cycles received, mean (SD); median (min, max)	[redacted]	[redacted]
Cumulative dose[c] (mg), mean (SD); median (min, max)	[redacted]	[redacted]
RDI[d] (%), mean (SD); median (min, max)	[redacted]	[redacted]
Subjects experiencing at least one dose interruption, n (%)	[redacted]	[redacted]
Subjects experiencing at least one dose decrease, n (%)	[redacted]	[redacted]
Induction phase	**N = 265**	**N = 268**
Treatment duration in weeks, [a] mean (SD); median (min, max)	[redacted]	[redacted]
Adjusted treatment duration [b] of study drug in weeks, mean (SD); median (min, max)	[redacted]	[redacted]
Number of cycles received, mean (SD); median (min, max)	[redacted]	[redacted]
Cumulative dose[c] (mg), mean (SD); median (min, max)	[redacted]	[redacted]
RDI[d] (%), mean (SD); median (min, max)	[redacted]	[redacted]
Consolidation phase	**N = 173**	**N = 175**
Treatment duration in weeks, [a] mean (SD); median (min, max)	[redacted]	[redacted]
Adjusted treatment duration [b] of study drug in weeks, mean (SD); median (min, max)	[redacted]	[redacted]
Number of cycles received, mean (SD); median (min, max)	[redacted]	[redacted]
Cumulative dose[c] (mg), mean (SD); median (min, max)	[redacted]	[redacted]

Category	Quizartinib	Placebo
RDI[d] (%), mean (SD); median (min, max)	[redacted]	[redacted]
Maintenance phase	**N = 116**	**N = 92**
Treatment duration in weeks, [a] mean (SD); median (min, max)	[redacted]	[redacted]
Adjusted treatment duration [b] of study drug in weeks, mean (SD); median (min, max)	[redacted]	[redacted]
Treatment duration of study drug in weeks in patients with protocol-specified HSCT, mean (SD); median (min, max)	[redacted]	[redacted]
Treatment duration of study drug in weeks in patients without protocol-specified HSCT, mean (SD); median (min, max)	[redacted]	[redacted]
Number of cycles received, mean (SD); median (min, max)	[redacted]	[redacted]
Cumulative dose[c] (mg), mean (SD); median (min, max)	[redacted]	[redacted]
RDI[d] (%), mean (SD); median (min, max)	[redacted]	[redacted]

Abbreviations: max, maximum; mg, milligram; min, minimum; RDI, relative dose intensity; SD, standard deviation.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: a. Treatment duration (days) for each phase = last dose date – first dose date + one within each phase. Treatment duration (days) overall = sum of treatment duration (days) in the three phases. b. Adjusted treatment duration (days) for each phase is the treatment duration minus the planned off drug days in each phase. Adjusted treatment duration (days) Overall = sum of Adjusted Treatment Duration (days) in three phases. c. Cumulative dose (mg) = cumulative amount of drug administered. d. RDI (%) = dose intensity/planned dose intensity × 100
Data cut-off date: 13 Aug 2021

B.2.10.2 Treatment-emergent adverse events

During the overall study period, most subjects experienced at least one TEAE (264 [99.6%] and 265 [98.9%] subjects in the quizartinib and placebo arms, respectively). Additionally, many subjects experienced at least one severe (grade ≥3, including grade 5) TEAE (244 [92.1%] and 240 [89.6%] subjects in the quizartinib and placebo arms, respectively) (21).

The most common TEAEs (≥10% of patients) of any grade generally occurred with similar frequencies in both treatment arms (21). Febrile neutropenia, pyrexia, diarrhoea and hypokalaemia were the TEAEs reported in the highest percentage of patients in both treatment arms (Table 35) (21).

In terms of severe TEAEs, the percentages of subjects with grade ≥3 (including grade 5) and grade 3 or 4 events were similar between the treatment arms (21). The most common grade 3 or 4 AEs (in ≥10% of patients) were febrile neutropenia, hypokalaemia and pneumonia in both groups and neutropenia in the quizartinib group. Severe thrombocytopenia was more frequent in subjects in the placebo group than the quizartinib group (Table 35) (21).

Myelosuppression and cytopenias were managed by transfusion, growth factor supports and dose modifications (21). Among patients with CR, median time to recovery of neutropenia (ANC ≥1000 cells per mm^3) was 36 days (IQR 29–44) in the quizartinib group and 29 days (IQR 27–38) in the placebo group. Median time to recovery of thrombocytopenia (platelet count ≥100,000 cells/mm^3) was 31 days (IQR 28–40) in the quizartinib group and 29 days (IQR 26–34) in the placebo group (21).

Within the grade 3 or 4 TEAEs that occurred in ≥3 % of subjects, the following grade 3 or 4 events occurred in at least twice as many subjects with quizartinib than with placebo: decreased appetite, ECG QT prolonged and rash. Conversely, grade 3 or 4 sepsis and hypocalcaemia events occurred in at least twice as many subjects taking placebo compared with quizartinib (21).

Febrile neutropenia in the quizartinib group and pneumonia and sepsis in both treatment groups were the only TEAEs with a higher percentage of patients reporting grade ≥3 events than grade 3 or 4 events. For all other TEAEs the percentage of patients with grade ≥3 events were the same as with grade 3 or 4 events.

Table 35. Summary of TEAEs, overall study period (safety analysis set)

Category	Quizartinib (N = 265)			Placebo (N = 268)		
	All grades[b] n (%)	Grade ≥3	Grade 3 or 4 n (%)	All grades[b] n (%)	Grade ≥3	Grade 3 or 4 n (%)
Subjects with TEAE[a]	**264 (99.6)**	**244 (92.1)**	**214 (80.8)**	**265 (98.9)**	**240 (89.6)**	**214 (79.9)**
Haematological TEAE						
Febrile neutropenia	117 (44.2)	[redacted]	115 (43.4)	113 (42.2)	[redacted]	110 (41.0)
Neutropenia	54 (20.4)	[redacted]	48 (18.1)	27 (10.1)	[redacted]	23 (8.6)
Thrombocytopenia	30 (11.3)	[redacted]	21 (7.9)	30 (11.2)	[redacted]	26 (9.7)
Anaemia	29 (10.9)	[redacted]	15 (5.7)	19 (7.1)	[redacted]	14 (5.2)
Neutrophil count decreased	27 (10.2)	[redacted]	23 (8.7)	12 (4.5)	[redacted]	9 (3.4)
Non-haematological TEAE						
Pyrexia	112 (42.3)	[redacted]	12 (4.5)	109 (40.7)	[redacted]	13 (4.9)
Diarrhoea	98 (37.0)	[redacted]	10 (3.8)	94 (35.1)	[redacted]	10 (3.7)
Hypokalaemia	93 (35.1)	[redacted]	50 (18.9)	96 (35.8)	[redacted]	44 (16.4)
Nausea	90 (34.0)	[redacted]	4 (1.5)	84 (31.3)	[redacted]	5 (1.9)
Headache	73 (27.5)	[redacted]	0	53 (19.8)	[redacted]	2 (0.7)
Rash	69 (26.0)	[redacted]	8 (3.0)	66 (24.6)	[redacted]	3 (1.1)
Vomiting	65 (24.5)	[redacted]	0	53 (19.8)	[redacted]	4 (1.5)
Stomatitis	57 (21.5)	[redacted]	12 (4.5)	56 (20.9)	[redacted]	8 (3.0)
Constipation	56 (21.1)	[redacted]	1 (0.4)	69 (25.7)	[redacted]	0
Cough	50 (18.9)	[redacted]	1 (0.4)	44 (16.4)	[redacted]	0
Abdominal pain	46 (17.4)	[redacted]	3 (1.1)	38 (14.2)	[redacted]	3 (1.1)
Decreased appetite	46 (17.4)	[redacted]	13 (4.9)	36 (13.4)	[redacted]	5 (1.9)
Alanine aminotransferase increased	42 (15.8)	[redacted]	12 (4.5)	27 (10.1)	[redacted]	13 (4.9)
Epistaxis	40 (15.1)	[redacted]	3 (1.1)	29 (10.8)	[redacted]	1 (0.4)
Pneumonia	39 (14.7)	[redacted]	30 (11.3)	41 (15.3)	[redacted]	30 (11.2)
Insomnia	37 (14.0)	[redacted]	0	30 (11.2)	[redacted]	0
Electrocardiogram QT prolonged	36 (13.6)	[redacted]	8 (3.0)	11 (4.1)	[redacted]	3 (1.1)

Category	Quizartinib (N = 265)			Placebo (N = 268)		
	All grades[b] n (%)	Grade ≥3	Grade 3 or 4 n (%)	All grades[b] n (%)	Grade ≥3	Grade 3 or 4 n (%)
Pruritus	35 (13.2)	[redacted]	2 (0.8)	40 (14.9)	[redacted]	0
Dyspepsia	30 (11.3)	[redacted]	1 (0.4)	23 (8.6)	[redacted]	2 (0.7)
Oedema peripheral	30 (11.3)	[redacted]	1 (0.4)	37 (13.8)	[redacted]	3 (1.1)
Hypomagnesaemia	30 (11.3)	[redacted]	1 (0.4)	30 (11.2)	[redacted]	1 (0.4)
Hypertension	29 (10.9)	[redacted]	13 (4.9)	33 (12.3)	[redacted]	18 (6.7)
Upper abdominal pain	29 (10.9)	[redacted]	3 (1.1)	25 (9.3)	[redacted]	2 (0.7)
Arthralgia	29 (10.9)	[redacted]	1 (0.4)	35 (13.1)	[redacted]	2 (0.7)
Fatigue	29 (10.9)	[redacted]	1 (0.4)	23 (8.6)	[redacted]	0
Aspartate aminotransferase increased	28 (10.6)	[redacted]	7 (2.6)	19 (7.1)	[redacted]	3 (1.1)
Hypophosphataemia	27 (10.2)	[redacted]	18 (6.8)	24 (9.0)	[redacted]	16 (6.0)
Oropharyngeal pain	27 (10.2)	[redacted]	0	18 (6.7)	[redacted]	1 (0.4)
Hypocalcaemia	26 (9.8)	[redacted]	2 (0.8)	29 (10.8)	[redacted]	8 (3.0)
Back pain	19 (7.2)	[redacted]	0	28 (10.4)	[redacted]	2 (0.7)
Sepsis	15 (5.7)	[redacted]	11 (4.2)	28 (10.4)	[redacted]	24 (9.0)

Abbreviations: QT, interval between the start of the Q wave and the end of the T wave; TEAE, treatment-emergent adverse event.
References: Erba et al. 2023 (21); Daiichi Sankyo, 2022 (73)
Notes: a. AEs regardless of causality. b. Only TEAEs that occurred in ≥10% of patients in the safety-analysis population of either group are presented.
Three patients in each group were not treated and are not included in the safety-analysis population. If a patient had more than one event, that patient was counted only once.
Data cut-off date: 13 Aug 2021

B.2.10.3 Study drug-related treatment-emergent adverse events

During the overall study period, a higher percentage of subjects in the quizartinib arm (160 [60.4%] subjects) experienced TEAEs that were assessed as related to study drug by the investigator compared with the placebo arm (97 [36.2%] subjects) (21).

The most common study drug-related TEAEs (≥5% of patients) assessed by the investigator as related to quizartinib treatment included cytopenias (neutropenia, thrombocytopenia, neutrophil count decreased, febrile neutropenia and anaemia), ECG QT prolonged, gastrointestinal disorders (nausea and diarrhoea), alanine aminotransferase increased and pyrexia (Table 36) (73).

In terms of severe study-drug related TEAEs, a higher percentage of subjects in the quizartinib arm experienced grade ≥3 and grade 3 or 4 TEAEs (118 [45%] and [redacted] subjects, respectively), assessed as related to study drug by the investigator, compared with the placebo arm (65 [24%] and [redacted] subjects, respectively) (21, 73). Cytopenias were the most frequently reported grade 3 or 4 TEAEs assessed by the investigator as related to quizartinib treatment (73). Of the grade 3 or 4 TEAEs occurring in ≥3% of subjects, the following events assessed as related to study drug by the investigator occurred in at least twice as many subjects with quizartinib than with placebo: neutropenia and neutrophil count decreased (73).

Table 36. Study drug-related TEAEs by PT, overall study period (safety analysis set)

Category	Quizartinib (N = 265)			Placebo (N = 268)		
	All grades[a] n (%)	Grade ≥3	Grade 3 or 4 n (%)	All grades[a] n (%)	Grade ≥3	Grade 3 or 4 n (%)
Subjects with study drug-related TEAE	**160 (60.4)**	[redacted]	[redacted]	**97 (36.2)**	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PT, preferred term; QT, interval between the start of the Q wave and the end of the T wave; TEAE, treatment-emergent adverse event.
References: Erba et al. 2023 (21), Daiichi Sankyo, 2022 (73)
Notes: a. Only study drug-related TEAEs that occurred in ≥5% of patients in the safety-analysis population of either group are presented.
If a subject had more than one event per PT level, the subject was counted once at each level of summation. PTs are sorted by decreasing frequency of events in the quizartinib arm.

B.2.10.4 Serious adverse events (SAE)

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; or was an important medical event. This type of AE was more frequently reported in the quizartinib group than the placebo group (54% vs. 46% respectively) (21). The most frequently reported types of SAEs, occurring in ≥3% of patients in both treatment arms, were infections (pneumonia, septic shock and sepsis), blood disorders (febrile neutropenia and thrombocytopenia) and pyrexia (Table 37) (21).

The majority of SAEs reported were not considered to be related to study drug by the investigator (Table 37) (21).

Table 37. Overview of SAE, overall study period (safety analysis set)

Category	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
SAE[a]	**143 (54)**	**123 (46)**
Febrile neutropenia	29 (10.9)	22 (8.2)
Pneumonia	17 (6.4)	15 (5.6)
Septic shock	11 (4.2)	8 (3.0)
Sepsis	10 (3.8)	14 (5.2)
Pyrexia	8 (3.0)	5 (1.9)
Thrombocytopenia	2 (0.8)	8 (3.0)
Study drug-related SAE[b,c]	**41 (15)**	**29 (11)**
Febrile neutropenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Myelosuppression	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]

Abbreviations: SAE, serious adverse event.
References: Daiichi Sankyo, 2022 (73); Erba et al. 2023 (21)
Notes: a. SAEs in ≥3% of subjects in either arm by preferred term. b. Study drug-related SAEs occurring in ≥1% of subjects in either arm by preferred term. c. Based on investigator-reported causality.
If a subject had more than one event per preferred term level, the subject was counted once at each level of summation. AEs were coded using the MedDRA Version 24.0.
Data cut-off date: 13 Aug 2021

SAEs associated with a fatal outcome occurred in 30 of 265 (11%) patients in the quizartinib group and 26 of 268 (10%) patients in the placebo group, with infections

being the most common cause in both arms (Table 38) (21). The early death rates (within 30 days) from the start of study drug administration (6% in the quizartinib group vs. 3% in the placebo group) were in line with reported early mortality rates in patients with newly diagnosed AML treated with chemotherapy alone (89, 90) or chemotherapy and an FLT3 inhibitor (10, 91, 92). The most common reason for these early deaths was infection, which are a known risk for patients with newly diagnosed AML receiving intensive chemotherapy. The subjects with early deaths were generally older and had worse performance status compared with the overall study population.

Table 38. SAEs associated with fatal outcomes and summary of early deaths

Category	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
SAE associated with fatal outcome	30 (11.3)	26 (9.7)
Drug related SAEs associated with fatal outcome[a]	4 (1.5)	4 (1.5)
Summary of early deaths[b]		
Deaths within 30 days of study drug initiation	[redacted]	[redacted]
Deaths within 60 days of study drug initiation	[redacted]	[redacted]

Abbreviation: SAE, serious adverse event.
References: Erba et al. 2023 (1)
Notes: a. Based on investigator-reported causality. b. During induction, 20 patients died in the quizartinib group, and 13 patients died in the placebo group.

B.2.10.5 TEAEs associated with dose discontinuation and modification

The percentages of subjects with TEAEs associated with study drug discontinuation, interruption and dose reduction were higher in patients treated with quizartinib (Table 39) (21).

Table 39. Adverse events leading to dose modification/discontinuation

Category	Quizartinib (N = 265)	Placebo (N = 268)
AEs associated with study drug discontinuation	54 (20.4)	23 (8.6)
AEs associated with study drug dose interruption	90 (34.0)	54 (20.1)
AEs associated with study drug dose reduction	50 (18.9)	17 (6.3)

Abbreviations: AE, adverse event
References: Erba et al. 2023 (21)
Notes: Data cut-off date: 13 Aug 2021

B.2.10.6 TEAEs by treatment phase

By treatment phase, the percentage of subjects reporting TEAEs were similar between the treatment groups in each treatment phase, although grade ≥3 TEAEs were

reported more frequently in the quizartinib arm than the placebo arm during the maintenance phase (73).

In all phases, higher percentages of subjects in the quizartinib arm reported TEAEs that were associated with study drug discontinuation, including those related to study drug, compared with the placebo arm. Higher percentages of subjects with TEAEs associated with study drug interruption or dose reduction in the quizartinib arm compared with the placebo arm were observed primarily during the maintenance phase (73).

The percentages of subjects with TEAEs associated with death as an outcome were numerically higher in the quizartinib arm than in the placebo arm during the induction and consolidation phases (19 [7.2%] subjects vs. 13 [4.9%] subjects and 8 [4.6%] subjects vs. 5 [2.9%] subjects, respectively), but numerically lower in the quizartinib arm than the placebo arm in the maintenance phase (3 [2.6%] subjects vs. 7 [7.6%] subjects, respectively) (73).

The type, frequency, and severity of TEAEs were generally similar between the quizartinib and placebo arms, during the induction and consolidation phases. The most frequently reported types of TEAEs during these phases were gastrointestinal disorders (diarrhoea, nausea, and vomiting), infections (pneumonia), hypokalaemia, pyrexia, febrile neutropenia, and rash. The proportion of patients experiencing severe grade ≥3 TEAEs was similar between the quizartinib and placebo arms in the induction and consolidation treatment phases. However, in the maintenance phase the proportion experiencing grade ≥3 TEAEs was higher in the quizartinib arm than in the placebo arm (78.4% vs. 57.6%). The most frequently reported types of TEAEs during the maintenance phase were infections, gastrointestinal disorders and cytopenias. These types of events, as well as events of ECG QT prolonged, were also the most frequently reported events associated with study drug discontinuation, interruption, and/or dose reduction during the maintenance phase (73).

Table 40. Overall summary of TEAEs by treatment phase (safety analysis set)

	Induction phase, n (%)		Consolidation phase, n (%)		Maintenance phase, n (%)	
	Quizartinib (N=265)	Placebo (N=268)	Quizartinib (N=173)	Placebo (N=175)	Quizartinib (N=116)	Placebo (N=92)
TEAEs	260 (98.1)	261 (97.4)	160 (92.5)	160 (91.4)	109 (94.0)	84 (91.3)
With CTCAE grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade ≥3 (including 5)	187 (70.6)	200 (74.6)	120 (69.4)	121 (69.1)	91 (78.4)	53 (57.6)
Associated with death as outcome	19 (7.2)	13 (4.9)	8 (4.6)	5 (2.9)	3 (2.6)	7 (7.6)
Associated with study treatment discontinuation	26 (9.8)	11 (4.1)	10 (5.8)	5 (2.9)	18 (15.5)	7 (7.6)
Associated with study treatment dose interruption	24 (9.1)	30 (11.2)	14 (8.1)	13 (7.4)	65 (56.0)	22 (23.9)
Associated with study treatment dose reduction	7 (2.6)	3 (1.1)	4 (2.3)	0	42 (36.2)	14 (15.2)
Study drug-related TEAE	102 (38.5)	77 (28.7)	50 (28.9)	48 (27.4)	85 (73.3)	34 (37.0)
With CTCAE grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade ≥3 (including 5)	56 (21.1)	43 (16.0)	34 (19.7)	26 (14.9)	62 (53.4)	16 (17.4)
Associated with death as outcome	2 (0.8)	1 (0.4)	2 (1.2)	2 (1.1)	0	0
Associated with study treatment discontinuation	7 (2.6)	2 (0.7)	4 (2.3)	2 (1.1)	12 (10.3)	3 (3.3)
Associated with study treatment dose interruption	8 (3.0)	14 (5.2)	6 (3.5)	5 (2.9)	46 (39.7)	11 (12.0)
Associated with study treatment dose reduction	3 (1.1)	1 (0.4)	2 (1.2)	0	32 (27.6)	8 (8.7)
SAE	75 (28.3)	66 (24.6)	59 (34.1)	54 (30.9)	39 (33.6)	34 (37.0)

	Induction phase, n (%)		Consolidation phase, n (%)		Maintenance phase, n (%)	
	Quizartinib (N=265)	Placebo (N=268)	Quizartinib (N=173)	Placebo (N=175)	Quizartinib (N=116)	Placebo (N=92)
With CTCAE grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade ≥3 (including 5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with death as outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with study treatment dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with study treatment dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study drug-related SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With CTCAE grade ≥3 (including 5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with death as outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with study treatment dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with study treatment dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CTCAE, common terminology criteria for adverse events; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Notes: If a subject reported one or more AEs, the subject was counted only once per subject level.
References: Daiichi Sankyo, 2022; Erba et al. 2023 (93)

B.2.10.7 Adverse events of special interest (AESI)

QT prolongation AEs were more frequent with quizartinib than placebo (Table 41) (21). Most QT prolongation AEs were manageable, from the clinical perspective, with quizartinib dose modification and correction of electrolyte abnormalities. QTcF prolongation of more than 500 milliseconds (ms) (severe events) on ECG was uncommon (six of 265 [2%] in the quizartinib group and two of 268 [1%] in the placebo group). There were no cases of torsade de pointes and two patients in the quizartinib group (none in placebo) had cardiac arrest with recorded ventricular fibrillation on ECG (21). In the quizartinib arm events of cardiac arrest with ventricular fibrillation occurred in subjects in the induction phase with the presence of other significant risk factors for cardiac arrythmia (e.g. hypokalaemia) (73).

Table 41. QTcF prolongation by central ECG and cardiac events by AE

Category	Quizartinib (N = 265) n (%)	Placebo (N = 268) n (%)
QTcF interval based on central ECG data (ms), n (%)		
New QTcF prolongation >450 ms	91 (34.3)	48 (17.9)
New QTcF prolongation >450 ms and ≤480 ms	73 (27.5)	43 (16.0)
New QTcF prolongation >480 ms and ≤500 ms	15 (5.7)	4 (1.5)
New QTcF prolongation >480 ms	20 (7.5)	6 (2.2)
New QTcF prolongation >500 ms	6 (2.3)	2 (0.7)
QTcF increase from baseline >30 ms	146 (55.1)	87 (32.5)
QTcF increase from baseline >60 ms	27 (10.2)	13 (4.9)
Select cardiac AEs related to QT prolongation and torsade de pointes, by AE preferred term, n (%)[a, b]		
ECG QT prolonged[c]	36 (13.6)	11 (4.1)
Cardiac arrest/ventricular fibrillation	2 (0.8)[d]	0
Ventricular tachycardia	1 (0.4)	1 (0.4)

Abbreviations: AE, adverse event; ECG, electrocardiogram; QT, interval between the start of the Q wave and the end of the T wave; QTcF, corrected QT interval by Fridericia's formula.
References: Erba et al, 2023 (21)
Notes: a. One patient (0·4%) died in their sleep (PT "death") in the quizartinib arm. b. Two patients (0·8%) discontinued quizartinib due to QT prolongation. c. Based on reported event, not central ECG data. d. Two patients (0·8%) treated with quizartinib had cardiac arrest (grade 4 [n=1], grade 5 [n=1]), with recorded ventricular fibrillation in the setting of severe hypokalaemia
According to the Common Terminology Criteria for Adverse Events grade 3 QTcF prolonged events include those where subjects have an average QTc ≥ 501 ms or where there is a >60 ms change from baseline (94). Grade 4 QTcF prolonged events include those where any of the following events occur: torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia (94).
Data cut-off date: 13 Aug 2021

Information on the other AESI – Combined Elevations of Aminotransferases and Bilirubin – can be found in the appendix F.

B.2.11 Ongoing studies

There are no ongoing studies of quizartinib relevant for this appraisal.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Key findings

The findings derived from the QuANTUM-First trial demonstrate that quizartinib is an effective and generally well-tolerated treatment option for newly diagnosed adult AML patients with *FLT3-ITD* mutation when administered with chemotherapy with/without HSCT, followed by maintenance monotherapy for up to 36 cycles.

Quizartinib resulted in a statistically significant and clinically meaningful improvement in OS, the primary endpoint of the QuANTUM-First trial, compared to placebo. Median OS was longer in the quizartinib group compared with standard therapy in the placebo group, resulting in a 16.8-month extension of median OS (31.9 months vs. 15.1 months, respectively). Subjects in the quizartinib arm had a 22.4% lower risk of death relative to subjects in the placebo arm (HR: 0.78; 95% CI: 0.62 to 0.98; 2-sided p=0.0324). The 3-year landmark analysis shows survival rates of 49.9% (95% CI: 43.7 to 55.9) for the patients in the quizartinib arm versus 41.1% (95% CI: 35.0 to 47.0) for the patients in the placebo arm. The improvement in OS favouring quizartinib over placebo was also observed in most prespecified subgroups. The results of the unstratified OS analysis were also consistent with those of the primary OS analysis with an HR of 0.774 (95% CI: 0.614 to 0.975; nominal p=0.0290). The analysis that censored patients who received HSCT showed a benefit of quizartinib over placebo that was not statistically significant with an HR of 0.75 (95% CI: 0.56 to 1.01; nominal p=0.0550). The OS benefit is considered to be established with reasonable certainty since other exploratory data (e.g. EFS following 56-day definition) support this effect. While exploratory, reliability of these endpoints was supported by several additional sensitivity analyses presented.

For the secondary endpoints, EFS was defined in three different ways: i) According to US FDA definition used in the primary analysis, ITF was defined as not achieving CR within 42 days from the start of the last induction chemotherapy; ii) The FDA's definition of ITF was applied with a 56-day window rather than a 42-day restriction; and iii) According to the initial protocol definition, ITF defined as not achieving CRc up to day 56. The primary analysis of the secondary endpoint was not statistically significant (preventing statistical analysis for the other secondary endpoints). However, using other definitions of EFS did show a statistically significant difference between the two treatment arms in favour of quizartinib. The median EFS per protocol definition, which is consistent with the recommendations from current AML guidelines, was 11.9 months vs 5.7 months, with a HR of 0.729 (95% CI: 0.592-0.897).

While CR rates were similar between treatment arms, CRc rates were numerically higher in the quizartinib arm (71.6%) compared with the placebo arm (64.9%), which was primarily driven by a higher rate of CRi in the quizartinib arm (21). During the study, a total of 102 (38.1%) subjects in the quizartinib arm and 91 (33.6%) subjects in the placebo arm underwent protocol-specified HSCT. This higher transplant rate in the quizartinib arm was likely driven by the higher CRc rate in the quizartinib arm. Despite similar rates of CR in the two treatment groups, responses were more durable when quizartinib was added to standard chemotherapy. The median duration of CR was three times longer in subjects in the quizartinib group than in the placebo group (38.6 months, 95% CI: 21.9 to NE vs. 12.4 months, 95% CI: 8.8 to 22.7; HR = 0.621, 95% CI: 0.451, 0.857) (76).

Exploratory analyses showed that median RFS for subjects achieving CR in the induction phase was approximately three times longer in the quizartinib arm compared with the placebo arm (39.3 vs. 13.6 months, respectively). These results are clinically meaningful and indicate that quizartinib may delay relapse or death in subjects who achieved CR. In a post-hoc analysis, subjects who achieved CR in the quizartinib arm also had numerically lower CIR rates than those in the placebo arm (31% vs. 43% respectively at 24 months).

In another post-hoc analysis of participants with CRc, it was found that quizartinib induced more MRD negativity and was associated with a 3-fold lower level of *FLT3-*

ITD MRD VAF compared with placebo (0.01% vs. 0.03%; nominal 2-sided p=0.0251). This highlights the potential long-term benefits of quizartinib as MRD has prognostic value in AML in terms of survival and relapse rates (95).

The QuANTUM-First study is the first study to explore the impact of quizartinib on QoL for adult patients with newly diagnosed *FLT3-ITD*+ AML. A clinically meaningful improvement was observed over time in both treatment arms compared to baseline in the EQ-5D-5L index UK value set (improvements were on average greater than MCIDs from treatment initiation in both arms), though this observation may be confounded by potential bias introduced by attrition of subjects in later timepoints. The analysis of PROs suggested that there is no detrimental impact on QoL resulting from the addition of quizartinib to standard of care chemotherapy in patients with newly diagnosed *FLT3-ITD*+ AML.

Quizartinib had a generally manageable safety profile, similar to what is expected for patients with newly diagnosed AML receiving standard intensive chemotherapy alone or chemotherapy and FLT3 inhibitors (10). AEs were managed through monitoring and dose modifications. No new safety concerns were identified in the study, and the types and severity of TEAEs were generally similar between both treatment arms. Infections, cytopenias, myelosuppression and QT prolongation, were the main safety risks identified. However, the incidence of serious infections and cytopenias was well balanced between treatment groups. Management of myelosuppression is part of the routine clinical practice for treatment of patients with newly diagnosed AML. Events associated with myelosuppression can be appropriately managed by transfusion and growth factor support, as well as through protocol-specified study drug dose modifications. Quizartinib is associated with QT prolongation in a dose-dependent and concentration dependent manner, as has been reported with other FLT3 inhibitors (96). Although the incidence of QT prolongation was higher with quizartinib than placebo, most events were asymptomatic and grade 1 or 2, and the incidence of grade 3 or worse QTcF prolongation overall was low, showing that QT prolongation with quizartinib is manageable with dose modification and correction of electrolyte abnormalities. The most frequent AE occurring during single-agent maintenance was neutropenia, which was manageable by dose reduction or interruption. The

percentage of patients with SAEs associated with fatal outcome was similar between treatment groups (11% and 10% in the quizartinib and placebo, respectively).

In summary, the findings from QuANTUM-First show that quizartinib could provide an effective and well tolerated treatment option for patients aged 18–75 years with newly diagnosed *FLT3-ITD*+ AML.

B.2.12.2 Strengths and limitations of the clinical evidence

Overall, the QuANTUM-First study was found to have a low risk of bias (see section B.2.5) and included a population that was representative of the general population of patients with newly diagnosed *FLT3-ITD*+ AML who are eligible to receive intensive induction therapy (21). The study population was well balanced between the two treatment arms (with similar baseline demographic and clinical characteristics). QuANTUM-First study was the first randomised pivotal study for *FLT3-ITD* (+) AML including elderly subjects eligible for intensive chemotherapy, a population for which there are still limited treatment options. The trial enrolled patients aged 18-75 years and approximately 40% of patients were between the ages of 60 to 75 years. This is line with the real-world AML population that has a median age at AML diagnosis of approximately 68 years (97). The study population of the RATIFY study – which analysed the safety and efficacy of midostaurin - was characterised by a more favourable prognosis than the one of the QuANTUM-First study because it was younger (no subjects were aged ≥60 years) and included approximately 22% of subjects with *TKD* mutations. The reduction in the risk of death of [redacted] observed with quizartinib in subjects aged <60 years compared with the 22% reduction observed with midostaurin in the same age group represents a treatment advancement for newly diagnosed *FLT3-ITD* (+) AML patients (10, 98).

Additionally, 53% of patients in the quizartinib arm and 52% of patients in the placebo arm of QuANTUM-First had an *NPM1* mutation, which demonstrates a similar rate of concurrent *NPM1* mutations compared with real-world populations (78). The study also allowed the safety of quizartinib to be evaluated in a patient population with risk factors for QT prolongation, to ensure the results were reflective of the general newly diagnosed *FLT3-ITD*+ AML patient population. Furthermore, there was a high enrolment of subjects from Europe (about 60%) hence subjects were likely to be

representative of patients in the UK. Aside from study validity another strength of this trial was the duration of follow-up, with a follow-up of up to almost four years. Consequently, data from the trial are sufficiently mature to demonstrate effects of quizartinib on OS as well as RFS and CIR.

Limitations of the study include the use of a placebo comparator group in QuANTUM-First, considering that midostaurin plus chemotherapy has been approved since 2017. However, when QuANTUM-First began in 2016, no *FLT3* inhibitor was approved for *FLT3*-mutated newly diagnosed AML and there was a lack of randomised data in people aged 60 years or older. Therefore, at that time, chemotherapy plus placebo was chosen as the appropriate comparator. Furthermore, the data monitoring committee reviewed the RATIFY data and recommended continuing the QuANTUM-First study as originally designed, maintaining the placebo group.

The findings from QuANTUM-First represent important progress in the management of patients aged 18-75 years with newly diagnosed *FLT3-ITD*+ AML.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR of cost-effectiveness studies in *FLT3*+ AML was conducted to identify published economic evaluations of interventions that could be used to address the decision problem and inform the economic model structure. The SLR identified eight unique cost-effectiveness models (CEMs) in *FLT3*+ AML from eight separate study references. Of these, three studies, addressing three models, were specific to the UK.

Two models specific to the UK applied a partitioned survival model whilst the third applied a decision-tree structure followed by partitioned survival models. Two of the models were specific to newly diagnosed patients. All three UK studies adopted a lifetime time horizon. None of the studies reviewed the cost-effectiveness of quizartinib in *FLT3*+ AML. A summary of the published UK based cost-effectiveness studies identified in the SLR, including analyses developed to inform recent NICE technology appraisals is presented in Table 42.

Full details of the studies identified, their methodology and study quality assessments are provided in Appendix G.

Table 42. Summary list of published UK cost-effectiveness studies

Study	Year	Summary of model	Patient population (median age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Tremblay 2018 (99)	2018	Partitioned-survival model Cycle time: 28-day Time horizon: lifetime	ND adult patients with *FLT3*+ AML (NR)	Midostaurin + chemo (7+3): 7.79 Chemo (7+3): 6.32	Midostaurin + Chemo (7+3): £267,325 Chemo (7+3): £213,253	£36,826
NICE TA523 (100)	2017	Partitioned-survival model Cycle time: 28-day Time horizon: lifetime	ND patients with *FLT3*+ AML (47)	Midostaurin + chemo (7+3): 7.79 Chemo (7+3): 6.32	NR	Midostaurin + chemo (7+3) vs chemo (7+3): • Base-case in original executable model (CS main submission): £34,327 per QALY • Base-case in updated executable model (CS response to clarification): £33,672 per QALY • Company's base case results - ERG's additional calculation correction implemented to CS updated model: £28,270 • ERG's preferred base case: £62,810 • ERG's base-case including revised model structure: £44,924

Study	Year	Summary of model	Patient population (median age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA642 (101)	2019	Decision-tree structure followed by partitioned survival models Cycle time: 1 month Time horizon: lifetime	Adult patients with *FLT3*+ R/R AML (62)	NR	NR	•Gilteritinib vs azacitidine: (deterministic): £44,663 •Gilteritinib vs azacitidine: (probabilistic): £41,755 •Gilteritinib vs FLAG-Ida (deterministic): £47,235 •Gilteritinib vs FLAG-Ida (probabilistic): £44,458 •Gilteritinib vs MEC (deterministic): £48,512 •Gilteritinib vs MEC (probabilistic): £45,377 •Gilteritinib vs LDAC (deterministic): £52,954 •Gilteritinib vs LDAC (probabilistic) £49,936 •Gilteritinib vs BSC (deterministic): £35,773 •Gilteritinib vs BSC (probabilistic): £31,205 •Gilteritinib vs weighted comparator (deterministic): £47,695 •Gilteritinib vs weighted comparator (probabilistic): £44,750

Abbreviations: AML, acute myeloid leukaemia; BSC, best supportive care; Chemo, chemotherapy; CS, company's submission; ERG, evidence review group; FLAG-Ida, fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; *FLT3*+, FMS-like tyrosine kinase 3 mutation positive; GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; LDAC, low-dose cytarabine; MEC, mitoxantrone, etoposide and cytarabine; ND, newly diagnosed; NICE, National Institute for Health and Care Excellence; NR, not reported; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; R/R, relapsed/refractory.

B.3.2 Economic analysis

The systematic literature review search of cost-effectiveness studies identified eight unique economic evaluations in *FLT3*+ AML. No relevant economic evaluations that provided estimates for the cost-effectiveness of quizartinib + SC in newly diagnosed *FLT3*+ AML were identified. Therefore, a de novo model was developed to assess the cost-effectiveness of quizartinib + SC, compared to other available treatments for adults with newly diagnosed *FLT3*+ AML (midostaurin + SC and SC alone). Herein quizartinib + SC and midostaurin + SC will be described as the quizartinib regimen and the midostaurin regimen respectively. Similarly, the SC treatment without a FLT3 inhibitor (*FLT3*i) will be referred to as the SC regimen (the full regimens are outlined in section B.3.5.1). The model was conceptualised based on the SLR of previous cost-effectiveness studies in *FLT3*+ AML (Appendix G) which included previous NICE technology appraisals of midostaurin (TA523) and gilteritinib (TA642).

B.3.2.1 Patient population

The patient population considered in the economic evaluation consists of adult patients with newly diagnosed *FLT3-ITD*+ AML who are eligible to be treated with intensive chemotherapy (i.e. standard cytarabine and anthracycline during induction and standard cytarabine consolidation chemotherapy). This patient population is consistent with the EMA licensed indication and anticipated Great Britain indication for quizartinib, and the decision problem considered in this submission (see Table 1). As described in Section B.2.8.4, to enable a meaningful comparison of the survival outcomes between quizartinib and midostaurin, the QuANTUM-First patient population is reweighted by matching on TEMs in the MAIC analysis. This adjustment ensures that the adjusted QuANTUM-First population (effectively a RATIFY-like QuANTUM-First population) aligns with the RATIFY population.

For scenario analyses using the trial data alone (direct pairwise trial-based comparison) and the outcomes of the ML-NMR, the full QuANTUM-First population was used. Methods and results for each can be read in Appendix M.

B.3.2.2 Model structure

The cost-effectiveness of quizartinib in newly diagnosed *FLT3-ITD*+ AML patients is evaluated using a Markov model. A schematic illustrating the model pathway is

outlined in Figure 21. The health states were selected to reflect the natural history of the disease and are consistent with previously published economic evaluations, technology appraisals and the QuANTUM-First trial. The model incorporates both 1L and second-line (2L) *FLT3-ITD*+ AML treatment. The model structure was designed to provide the flexibility to incorporate additional health states to address the limitations of the partitioned survival model used in TA523 highlighted by the NICE committee.

Table 43. Descriptions of the model health states.

Health state	Description
Induction	Patients enter the model in the 'induction' health state, where they remain for a maximum of two cycles. Patients can move from induction to the 'CR1','relapse1', 'refractory' or 'death' health states. In this health state patients receive induction treatment in line with their assigned treatment regimen.
Complete remission in 1L (CR1)	After induction, patients who achieve CR or CRi enter the 'CR1' health state. On entering 'CR1', patients start consolidation treatment for up to four cycles. Those who complete the consolidation treatment will continue to take maintenance treatment in the 'CR1' health state, which lasts up to 36 cycles for the quizartinib regimen, and up to 12 cycles for the midostaurin regimen. Patients may reside in this health state after the maximum treatment duration. Patients are allowed to transition into the 'HSCT 1L' health state once they entered the 'CR1' health state (i.e. patients may transition into the 'HSCT 1L' health state at any point before completion of consolidation and maintenance treatment). Patients can relapse during any cycle of either phase of 'CR1' and so they may not complete the full number of consolidation and maintenance treatment cycles. To capture patient transitions accurately, there are two cohorts of patients entering 'CR1': those who responded after one cycle of induction, and those that responded after two cycles. Therefore, the 'CR1' state has been split into two states within the model, so that those who transition after a second round of induction have the correct time in state TPs and costs applied.
Refractory	Patients who fail to achieve CR1 in response to induction therapy move to the refractory health state. These patients will receive 2L treatment. Those who do not achieve CR or CRi, even those who experience a partial response to treatment, are all assumed equivalent to refractory patients (i.e. patients who do not achieve CRc).
Relapse	Patients who achieve CR (and thus enter 'CR1') but who then relapse enter the 'relapse1' health state. These patients will receive 2L treatment and if they achieve CR again, transition to 'CR2'. 2L treatments in the model include FLAG-Ida (a

Health state	Description
	combination of fludarabine, cytarabine, idarubicin, and G-CSF) or gilteritinib.
HSCT	Patients can only enter 'HSCT 1L' after achieving complete remission (CRc) in first line (i.e. enter 'HSCT 1L' from 'CR1'). To align with the clinical pathway, for patients who undergo HSCT, maintenance therapy is allowed to begin after 4 cycles following entry into the 'HSCT 1L' state. Patients will remain in this state until they experience relapse or die.
Post-HSCT relapse	Patients who relapse post-HSCT 1L are not allowed to undergo another HSCT, although they are allowed to receive 2L treatment. Patients are assumed to remain in the 'post-HSCT relapse' state until they die.
Complete remission in 2L (CR2)	Patients who did not respond to induction therapy or whose response has waned (e.g. those in the refractory or relapse1 states) but respond (CR or CRi) to 2L treatment will enter 'CR2'. Patients will remain in the 'CR2' state until they receive HSCT, relapse, or die.
Relapse 2L (Relapse2)	Patients who relapse after either entering the 'CR2' health state or after having an HSCT in 2L enter the 'relapse2' health state. Patients who enter this state remain here until they die, 3L treatment is not modelled.
HSCT 2L	Patients can only enter HSCT after complete remission in second line (i.e. enter 'HSCT 2L' from 'CR2'). This consists of 13 tunnel states: • 'HSCT', which lasts three cycles (representing the period while the procedure of transplantation occurs; patients are not receiving quizartinib or comparators during this time) • 'HSCT recovery', which represents the period of recovery after transplant and lasts ten cycles during which the maintenance treatment can begin. These tunnel states align with the clinical pathway of patients receiving HSCT. Tunnel states were used within the HSCT pathway to facilitate time-dependent variation in costs and utilities for the procedure and the recovery period.
Post-HSCT maintenance 2L	Following the transplant tunnel states, patients can enter maintenance treatment in 2L. This state represents the period following HSCT during which patients maintain response. Patients will remain in this state until they experience a relapse or die.
Death (absorbing state)	Patients from all health states can die at any point within the model.

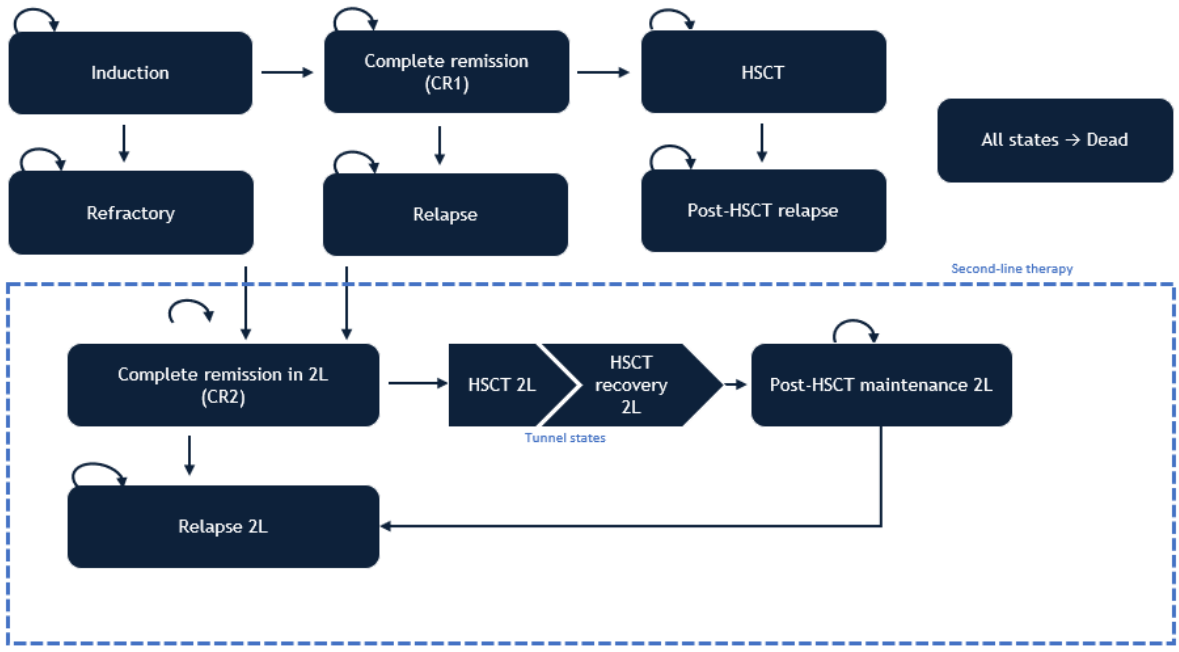
Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; CRi, CR with incomplete neutrophil or platelet recovery; CR1, first CR; CR2, second CR; FLAG-Ida, fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; G-CSF, granulocyte colony stimulating factor; HSCT, haematopoietic stem cell transplantation; relapse1, first relapse; relapse2, second relapse; SC, standard chemotherapy; 1L, first-line treatment; 2L, second-line treatment; TP, transition probability.

The model features and the corresponding justification are outlined in Table 44. A state transition cohort model has been adopted to facilitate the incorporation of additional health states compared to TA523, this accounts for the committee's critique of the midostaurin model as outlined in Table 44.

The perspective used for this analysis is that of the NHS and Personal and Social services (PSS) in England and Wales and a lifetime horizon was applied in line with the NICE reference case. We assumed that patients would live to maximum of 100 years, thus subtracting the mean patient age of 47 years equates to a maximum remaining lifetime for the MAIC adjusted population of 53 years. Over this time horizon, costs and effects were discounted at a rate of 3.5% per annum in line with the NICE reference case (102). The modelled cost year was 2022.

A cycle length of 28 days was used to align with the treatment cycle length of quizartinib in the QuANTUM-First trial. This is also in line with previous AML models which had cycle lengths ranging from 28 days to one month (see Appendix G). A cycle length of 28 days remains sensitive enough to shorter term changes in patient status. A half-cycle correction was applied to adjust for the distribution of costs and benefits accrued within each cycle.

Figure 21. Model schematic



Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; CR1, first CR; CR2, second CR first-line treatment; 2L, second-line treatment.

Table 44. Features of the economic analysis

Factor	Previous submission: TA523	Current evaluation, chosen values	Justification
Model framework	Partition survival	Markov model	• In the TA523 model, patients who failed to respond or relapsed following first-line therapy moved to the relapsed health state. Once patients entered the relapse state, it was assumed that patients could not achieve CR and could only move to the HSCT or death state. In terms of modelling 2L treatments, patients who relapsed or failed to achieve CR would receive 2L treatment in this health state. However, the model did not capture the benefit of 2L treatment and allow patients to move into the CR state. All patients remaining in the relapse health state were assumed to have the same HRQoL and accrue the same costs. The ERG argued that the limited ability of the model to capture effects of 2L treatment had a significant impact on the model, leading it to underestimate the ICER. • To rectify this problem in the quizartinib model, subsequent therapies up until 2L treatment have been included. Furthermore, to avoid patients on subsequent treatment remaining in the relapse state, an additional health state (CR2) has been included so that the model can distinguish between patients who respond to 2L treatment and those who do not in terms of costs, QALYs and disease progression. A Markov model was a more suitable model framework to incorporate these adjustments.
Cure modelling	A cure point of about 6.2 years (80 cycles in the model) was applied in the company submission	A cure point of three years (40 cycles in the model) was applied	• In TA523 the ERG noted that the cure point used by the company was an arbitrary assumption and the clinical experts stated that they would expect anyone whose disease was still in remission after 5 years to be cured. The committee concluded that, of the analyses presented by the company and the ERG, surviving patients with relapsed disease entering a cured health state after 3 years was the most appropriate method to overcome the model's restriction on people in the relapsed state and to better reflect clinical practice in England (103). The committee considered that it would prefer to use the latest point at which the data showed a levelling out effect because this was more logically a point of 'cure' (6). Similarly, in TA642 the committee concluded that a cure point between 2 years and 3 years was plausible (104). • In the quizartinib model three years was selected as the cure point as, in line with the feedback from the NICE committee on TA523 (105), a levelling out effect was observed at this time. A three-year cure point was also in line with feedback from clinical experts.

Factor	Previous submission: TA523	Current evaluation, chosen values	Justification
Health states	• AML diagnosis/induction • CR • Relapse • SCT • Death	• Induction • Complete remission (CR1) • HSCT • Post-HSCT relapse • Refractory • Relapse • Complete remission in 2L (CR2) • HSCT 2L (tunnel states) • Post-HSCT maintenance 2L • Relapse 2L • Death (absorbing state)	• The rational for the addition of CR2 is described in the 'model structure' row. • In TA523, the ERG noted that patients who fail to respond to induction therapy (i.e. refractory) were grouped together with patients who relapse after achieving CR and as such it was not possible to distinguish between these two groups of patients. The assumption was made that the costs and health-related quality of life (HRQoL) for patients who are primary refractory and patients who relapse were the same. In the quizartinib model, refractory disease and relapsed disease are modelled as two separate health states which allows different costs and utilities to be input. • An additional health state (post-HSCT relapse) has been incorporated in the quizartinib model to account for patients relapsing after HSCT. Patients who relapse after HSCT do not enter the same relapse state as those who relapse out of CR. Whilst HSUVs are equal, this approach ensures patients do not receive a second HSCT in the model (according to clinical expert opinion a negligible number of patients would receive a second HSCT in AML).
HSCT Tunnel states	HSCT tunnel states: • HSCT treatment • HSCT recovery • Post-HSCT recovery.	HSCT single state HSCT 2L tunnel states: • HSCT • HSCT recovery.	• In the RATIFY trial, patients who underwent HSCT were not to continue midostaurin or placebo. However, in the QuANTUM-First trial, patients who underwent HSCT could continue with quizartinib or placebo as a maintenance therapy. To capture the mortality data from the QuANTUM-First trial, a single health state, 'HSCT 1L', was modelled for 1L HSCT • The HSCT 2L data was not captured by the QuANTUM-First trial. To keep consistency with the previous NICE TA523, the tunnel states have been established for HSCT 2L. • In the midostaurin NICE submission model, an assumption was made that patients who entered the HSCT health state could either remain in post-HSCT recovery or transition to death. The ERG debated this assumption on the basis that the literature suggests that between 25% to 40% of patients relapse following HSCT. The midostaurin model also failed to take into account the lower utility associated with a relapse following HSCT. • Based on this information, the model structure developed for quizartinib includes post-HSCT maintenance as an additional health state (rather than retaining it within the tunnel states) and HSCT relapse as an additional health state to account for patients relapsing after HSCT.
Time horizon	Lifetime	Lifetime	Consistent with TA523 and the NICE reference case (this is sufficient to capture all meaningful differences in technologies compared)
Cycle length	28-day	28-day	Consistent with TA523 and matches the typical treatment cycle length of quizartinib in the QuANTUM-First trial

Factor	Previous submission: TA523	Current evaluation, chosen values	Justification
Discount for utilities and costs	3.5%	3.5%	Consistent with TA523 and the NICE reference case
Perspective	NHS and PSS	NHS and PSS	In line with the reference case
Source of utilities	Published utilities from Uyl-de Groot et al., Batty et al., Leunis et al., Pan et al. and Grulke et al., were applied for all health states.	Published utilities from Uyl-de Groot et al., Batty et al., Leunis et al., Pan et al. and Grulke et al., were applied for all health states.	NA
Source of costs	Drug costs: Data on file, BNF	Drug costs: Data on file, BNF 2023, eMIT 2023	NA
	Routine care costs: PSSRU, NHS reference costs	Routine care costs: PSSRU, NHS reference costs and TA523	NA
	Treatment monitoring costs: Celgene HCRU questionnaire	Treatment monitoring costs: TA523, NHS reference costs, NIHR iCT, PSSRU	Treatment monitoring costs were sourced from the NHS reference costs and the NIHR tariff in the quizartinib model as these were more recent than those used in TA523 which were based on a questionnaire in a 2016 NICE submission (TA399: Azacitidine for treating AML with more than 30% bone marrow blasts). The costs used in the quizartinib model are higher than those used in the midostaurin model but are more in line with those used in the gilteritinib model (TA642).
	HSCT costs: NHS reference costs	HSCT costs: NHS reference costs	NA
	Terminal care costs: Georghiou, Theo, and Martin Bardsley. "Exploring the cost of care at the end of life." Report, Nuffield Trust, London (2014)	Terminal care costs: PSSRU	More recent data were available from PSSRU for terminal care costs
	Adverse event costs: NHS reference costs	Adverse event costs: TA523, NHS reference costs	NA

Abbreviations: HSCT, allogeneic stem cell transplantation; AML, acute myeloid leukaemia; BNF, British National Formulary; CR, complete remission; CR1, first CR; CR2, second CR; eMIT, electronic market information tool; ERG, evidence review group; HCRU, healthcare resource utilisation; HRQoL, health related quality of life; ICER, incremental cost-effectiveness ratio; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; NIHR iCT, National Institute for Health and Care Research, interactive costing tool; OS, overall survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; RFS, relapse-free survival; SCT, stem cell transplantation; TA, technology appraisal;relapse1, first relapse; relapse2, second relapse; 1L, first-line treatment; 2L, second-line treatment; TPs, transition probabilities.
References: NICE, 2013(102); NICE, 2016 (106); NICE, 2018 (6); NICE, 2018 (105); NIHR, (107)NHS, 2022 (108); PSSRU, 2022 (109) Pan et al.2010 (110); Uyl-de Groot et al.1998 (111); Batty et al. 2014 (112); Leunis et al. 2014(50); Grulke et al. 2012 (113).

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention in the model is quizartinib in combination with standard cytarabine and anthracycline (daunorubicin or idarubicin) induction chemotherapy, followed by quizartinib in combination with standard cytarabine consolidation chemotherapy (with or without HSCT) and then quizartinib single agent maintenance therapy was also permitted (1). As previously indicated this regimen will be referred to as the 'quizartinib regimen' and reflects that of QuANTUM-First as described in section B.2.3 and quizartinib's anticipated licenced indication. The trial protocol allowed for quizartinib to be given as maintenance treatment both upon CR without HSCT or following HSCT, which is replicated in the model. The detailed dosing schedule used in the model is presented in section B.3.5.1.

B.3.2.3.2 Comparators

Comparators considered in the cost-effectiveness analysis are in line with NICE recommendations and include the comparators in the final NICE scope:

- The 'midostaurin regimen': midostaurin + chemotherapy (daunorubicin + cytarabine) in the induction phase, midostaurin + chemotherapy (cytarabine) in the consolidation phase and then midostaurin single agent maintenance therapy was also permitted for patients who achieve CR but did not receive HSCT. This reflects the RATIFY trial and the UK midostaurin SmPC (10, 114)
- The 'Standard Chemotherapy' or 'SC regimen': chemotherapy in the induction phase with cytarabine plus daunorubicin or idarubicin, followed by consolidation with high dose cytarabine which reflects the chemotherapy option in the placebo arm of QuANTUM-First.

The dosing schedule for each of these comparators used in the model is presented in section B.3.5.1.

AML is the most frequent indication for HSCT (43). Despite its central role in the management of adult AML, only a minority of patients for whom transplantation is indicated undergo the procedure. Reasons for underutilisation include biologic factors, personal and physician choice, and lack of access. HSCT is considered the only

curative therapy for patients with primary refractory disease and offers the best chance for cure in those who relapse after initial chemotherapy. Whilst HSCT is not a comparator intervention in the model, the objective of the evaluated treatment regimens is often to bridge to a HSCT. Thus it is included in the model as an important aspect of clinical intervention and management. The HSCT transition probabilities (TPs) (in 1L and 2L) used in the model and the unit cost of HSCT are presented in section B.3.3.2.2, B.3.3.2.4 and B.3.5.4, respectively.

B.3.3 Clinical parameters and variables

B.3.3.1 Patient baseline characteristic

The baseline characteristics for the modelled population were derived from the QuANTUM-First trial population (intervention and control arms). As described in section B.3.2.1, the adjusted population of QuANTUM-First is used in the model base case to match the with the RATIFY population. Baseline patient characteristics for the modelled population included age, gender distribution, weight, height, and body surface area (BSA). Age and gender distributions are used to adjust the life tables which control background mortality events in the model. Mean height and mean bodyweight from the QuANTUM-First adjusted population were used to calculate mean BSA. BSA is considered within the dosing calculations for some of the chemotherapy treatment regimens. The baseline patient characteristics used in the model are presented in Table 45. This population was the basis of the fully incremental cost-effectiveness analysis, so was used to evaluate all comparisons across the three regimens; including where hazard ratios were the product of the MAIC.

Table 45. Baseline characteristics of patient population in the model

Patient population: Adjusted QuANTUM-First population	
Female	54.4%
Male	45.6%
Age at start (years)	47.0
Mean bodyweight (kg)	[redacted]
Mean height (cm)	[redacted]
Mean BSA (m^2)	[redacted]

Abbreviations: BSA, body surface area.
References: Erba et al. 2023 (21); Daiichi Sankyo, 2023 (85).

B.3.3.2 Time invariant transition probabilities

TPs for patients moving between the health states are based on IPD analyses of the QuANTUM-First adjusted population (115), published literature values and the MAIC analysis.

For generating health state membership from the trial data, each health state was defined as follows:

- Induction: all patients are assumed to start in the Induction health state, with Day 1 corresponding to the first day of the induction phase
- First complete remission (CR1): defined as the first day CRc was confirmed by an independent assessor
- Relapse1: defined as the first day relapse was observed by an independent assessor, after the patient had been observed to have a CRc by an independent assessor
- Refractory: defined as no response being confirmed by an independent assessor at the end of the induction period
- HSCT 1L: for patients in CR1, the date of patients receiving the conditioning regimen for HSCT.

The methods for deriving time invariant TPs for each health state are detailed in the following sections. The time-varying TPs based on time to event outcomes from the QuANTUM-First trial are described in section B.3.3.3. The MAIC results which are used to determine relapse from CRc and death from CRc for the midostaurin regimen are also reported in section B.3.3.3.

B.3.3.2.1 Transitions from induction

For the quizartinib and SC regimens, TPs from the induction health state were derived from QuANTUM-First trial data. Patients in the induction state can transition to CR1, Refractory, Death or remaining in the Induction state for a second cycle of induction treatment (maximum of 2 cycles).

The definition of the CR1 heath state in the model is in line with the QuANTUM-First trial definition of CRc, which is the percentage of subjects achieving CR or CRi after induction:

- CR: >1,000 neutrophils, >100,000 platelets, <5% blasts, no EMD, no Auer rods and an absence of leukaemic blasts in the peripheral blood by morphological examination)
- CRi: CR with incomplete platelet recovery (>1,000 neutrophils, ≤100,000 platelets, <5% blasts) or CR with incomplete neutrophil recovery (≤1,000 neutrophils, >100,000 platelets, <5% blasts).

The CRc was used in the model to align with the response criteria more relevant for clinical practice, as confirmed by UK medical experts.

Same as the QuANTUM-First trial definition, refractory in the model is defined as:

- CR never achieved in the induction phase within a 42-day window from the start of the last induction cycle; or
- Blasts <5% if Auer-rod positive; or
- Appearance of new or worsening extramedullary disease.

TPs from the induction health state to CR1, Refractory, and the Death health state were calculated based on the proportion of patients who had CRc, refractory disease, and death events during the first and second induction rounds in the adjusted QuANTUM-First population. The most severe health event that occurred to patients within the observed time frame was considered for estimation. For example, if a patient relapsed and died in the same cycle, the patient was counted as deceased, not relapsed, in that cycle to avoid double counting.

Transitions were calculated based on the number of patients in induction at the start of each round. The weighted number of patients used to calculate the TPs are presented in Table 46.

Table 46. Number of patients transitioning out of Induction, per induction cycle based on the adjusted QuANTUM-First population

Induction cycle	Transition to:	Number of patients	
		Quizartinib (n=[redacted])	SC (n=[redacted])
First induction cycle	Second induction round	[redacted]	[redacted]
	First CR	[redacted]	[redacted]
	Refractory	[redacted]	[redacted]
	Dead	[redacted]	[redacted]
		Quizartinib (n=[redacted])	SC (n=[redacted])
Second induction cycle	First CR	[redacted]	[redacted]
	Refractory	[redacted]	[redacted]
	Dead	[redacted]	[redacted]

Abbreviations: CR, complete remission; SC, standard chemotherapy treatment arm.
Reference: Daiichi Sankyo, 2022 (98)

TPs were calculated as the quotient of the number of patients transitioning to the new health state and the total number of patients in that cycle of induction (e.g. [redacted] for the transition to CR 1L in the quizartinib regimen for the first induction cycle). It was assumed that the CR events, which occurred after exceeding 56 days (i.e., two induction cycles) in the QuANTUM-First, happened in the second round of induction in the model.

In the RATIFY study, by design and protocol, only results based on CR were reported; CRi was not collected as at the time of the study and the concept of haematological recovery was not established. Consequently, as described in section B.2.8, the MAIC was restricted to comparing the rates of CR (rather than CRc). This approach excludes patients with CRi from the MAIC analysis, potentially leading to an underestimation of quizartinib's efficacy, if we consider the following evidence:

The CR and CRc response criteria are largely aligned, except for the requirement in CR to have achieved both platelet and neutrophil recovery. However, advice from UK clinical experts noted the primary measure of a successful response is not the count of platelets or neutrophils, but rather the response in terms of blast clearance. The status of the bone marrow, being the primary site of blood cell production and typically the area most affected by leukaemia, is crucial in determining whether a response has occurred. Thus, the absence of signs of leukaemia in the bone marrow would indicate a positive response to the treatment, even if full hematologic recovery has not yet

occurred. This is substantiated by a post-hoc analysis from the QuANTUM-First study (116), where [redacted] and [redacted] of subjects with CRi in the induction phase proceeded to receive the consolidation treatment and/or HSCT in the quizartinib and placebo arms, respectively.

Furthermore, clinical guidelines have highlighted that the CR rate is impacted by the time of measurement. The 2022 ELN guideline (8) states that 'To recognize the potential for continuing improvements in blood counts after myelosuppressive therapy, response definitions for patients with marrow blast clearance (<5%) may be adjusted to reflect the best hematologic response achieved prior to commencement of the next treatment cycle. Aspirate reports that include MLFS, CRh, or CRi should note the potential for post-marrow blood counts to alter the final response designation.' In clinical practice, CR is typically assessed at the scheduled time, such as during a planned bone marrow biopsy, even if platelet or neutrophil recovery has not yet occurred. In the majority of these cases, patients will soon or eventually recover platelet and neutrophil counts but will still be recorded as CRi. This is demonstrated by a QuANTUM-First post-hoc analysis, which found that [redacted] and [redacted] of subjects with CRi in the induction phase achieved CR by consolidation Cycle 1 Day 1 in the quizartinib and placebo arms, respectively (116). This indicates that patients reported with CRi in the quizartinib arm were in many cases effectively CR by commencement of consolidation treatment, which supports the CR/CRc transposition assumption underlying the ITC. It also conservatively positions quizartinib in the comparison with SC, which reported fewer CRi cases at the end of induction.

Therefore, to incorporate the comparative efficacy data from the MAIC into the model, it was deemed appropriate to assume that the relative treatment effect of midostaurin (vs quizartinib) was the same for CR and CRc.

As presented in section B.2.8, the MAIC of CR between quizartinib and midostaurin based on the adjusted QuANTUM-First population and RATIFY *FLT3-ITD* populations showed numerically unfavourable but not statistically significantly different outcomes with quizartinib as compared to midostaurin (OR: [redacted]; 95% CI: [redacted] to [redacted]) (85). For the midostaurin regimen, TPs of induction to first CR (1st and 2nd rounds of induction) were derived by combining the OR estimates from the MAIC with the TPs for the

reference treatment (i.e. quizartinib). For the transitions from induction to the 'refractory' or 'dead' states, in the absence of a comparative estimate, an assumption was made that these transitions were equal to those of quizartinib.

Table 47. Transition probabilities for AML diagnosis and induction, by induction round and treatment arm

Induction round	Transition to:	Transition probability, %					
		Quizartinib regimen		SC regimen		Midostaurin regimen	
		Inputs	Reference[a]	Inputs	Reference[a]	Inputs	Reference
First induction cycle	Induction	Residual	Residual	Residual	Residual	Residual	Residual
	First CR	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	MAIC analysis. See more detail in section B.2.8
	Refractory	[redacted]	Weighted population ([redacted] of [redacted] patients had refractory disease within 28 days)	[redacted]	Weighted population ([redacted] of [redacted] patients had refractory disease within 28 days)	[redacted]	Assumed equal to quizartinib arm
	Dead	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Assumed equal to quizartinib arm
Second induction cycle	Induction	0.0	All patients which require longer than 29 days to transition are moved out of induction at this cycle	0.0	All patients which require longer than 29 days to transition are moved out of induction at this cycle	0.0	All patients which require longer than 29 days to transition are moved out of induction at this cycle
	First CR	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] achieved CRc)	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] achieved CRc)	[redacted]	MAIC analysis. See more detail in section B.2.8
	Refractory	Residual	Residual	Residual	Residual	Residual	Residual
	Dead	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] died)	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] died)	[redacted]	Assumed equal to quizartinib arm

Abbreviations: AML, acute myeloid leukaemia; CR, complete remission; CRc, composite complete remission; MAIC, matching-adjusted indirect comparison; SC, standard chemotherapy treatment arm, NA, not applicable.
Reference: Daiichi Sankyo, 2022(98); Rucker et al. 2022 (84)
Notes: a. the data described in this column is from QuANTUM-First.

B.3.3.2.2 Transitions from CR1

The inputs of transitions from CR1 are summarised in the Table 49.

TPs from CR1 to Relapse1 and Death are time-variant and were derived from relapse after CRc and survival after CRc data from adjusted QuANTUM-First (quizartinib) population and the MAIC analysis (SC and midostaurin). The survival curves informing these TPs are presented in section B.3.3.3.

Due to the lack of data and discrepancies in the definition of remission in the QuANTUM-First and RATIFY trials, the HSCT rate could not be included as an endpoint in the MAIC. Therefore, the proportion of patients receiving HSCT was modelled as a function of complete response. This assumes that a fixed proportion of patients who achieve complete remission will proceed to protocol-specified HSCT and the transplant rate will not be affected by other factors, including the treatment received. The clinical plausibility of this assumption is supported by the QuANTUM-First trial data. As demonstrated in Table 48, there is a comparable proportion of patients who underwent the protocol-specified HSCT transplant among those after achieving CR or CRc. This proportion remains consistent when comparing the quizartinib and placebo arms.

Table 48. Analysis of protocol-specified HSCT rate in QuANTUM-First

	Quizartinib (n=268)	Placebo (n=271)
Patients achieving CRc	192 (71.6%)	176 (64.9%)
Patients achieving CR	147 (54.9%)	150 (55.4%)
Patients receiving protocol specified HSCT[a]	[redacted]	[redacted]
Patients receiving protocol-specified HSCT[a] after CRc per IRC assessment	[redacted]	[redacted]
Patients receiving protocol-specified HSCT[a] after CR per IRC assessment	[redacted]	[redacted]

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; AML: acute myeloid leukaemia; CR, complete remission; CRc.
composite complete remission; IRC, independent review committee.
Notes: a. Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens).

The transition from CR1 to HSCT 1L was based on the proportion of patients receiving protocol-specified HSCT after achieving CRc, as per the QuANTUM-First ITT analysis set (Table 48). A pooled rate of protocol-specified HSCT after achieving CRc was derived ([redacted]) and applied to all three interventions in the model. Therefore, the

modelled transplant rate for each treatment is only dependent on the proportion of patients in the CR1 health state at the time of HSCT.

The model was developed to transition all patients to HSCT in cycle 4. This assumption was based on the QuANTUM-First study (117) where HSCT was performed in CR1 after a median time of 3.5 months (equivalent to 3.8 model cycles) in the quizartinib arm and 3.3 months (equivalent to 3.5 model cycles) in the placebo arm.

Table 49. Transition probabilities from CR1, by treatment arm

Transition from:	Transition to:	Transition probability, %					
		Quizartinib		SC		Midostaurin	
		Inputs	Reference	Inputs	Reference	Inputs	Reference
CR1	CR1	Residual	Residual	Residual	Residual	Residual	Residual
	R1	Relapse from CRc curve from adjusted QuANTUM-First (CRc cohort of ITT)	QuANTUM-First trial data. Refer to section B.3.3.3 for more details	Combing HR from MAIC with the reference treatment (i.e. quizartinib)	MAIC analysis (B.2.8)	Combing HR from MAIC with the reference treatment (i.e. quizartinib)	MAIC analysis (B.2.8)
	HSCT 1L (per cycle for 4 – cycles)	[redacted]	DSE Q-F DOF, 2023. Data was pooled from quizartinib and SC (placebo) arm. Out of the 268 and 271 patients in the quizartinib and SC arm, [redacted] and [redacted] patients underwent protocol-specified HSCT after achieving CRc, respectively.	[redacted]	As per the quizartinib regimen	[redacted]	As per the quizartinib regimen
	Dead (time-varying)	Death from CRc curve from adjusted QuANTUM-First (censored for HSCT)	QuANTUM-First trial data. Refer to section B.3.3.3 for more details	Combing HR from MAIC with the reference treatment (i.e. quizartinib)	MAIC analysis (B.2.8)	Combing HR from MAIC with the reference treatment (i.e. quizartinib)	MAIC analysis (B.2.8)

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; CR1, first CR; DSE, Daiichi Sankyo Europe; DOF, data on file; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; ITT, intent-to-treat; OS, overall survival; Q-F, QuANTUM-First; RFS, relapse-free survival; SC, standard chemotherapy; 1L, first-line treatment.
Reference: Daiichi Sankyo, 2022 (98); Daiichi Sankyo, 2022 (73)

B.3.3.2.3 Transitions from HSCT (1L and 2L)

The transitions from HSCT 1L to death are time-variant and were derived from post protocol-specified HSCT survival in the adjusted QuANTUM-First population. The survival curves that inform these TPs are presented in the section B.3.3.3.

Very few patients who received protocol-specified HSCT after achieving CRc subsequently relapsed ([redacted] in the quizartinib arm and [redacted] in the placebo arm) in the QuANTUM-First ITT analysis set (116). Due to this immaturity of the data, the time-varying survival for post-HSCT 1L relapse was too uncertain to be informative. Therefore, time-invariant inputs sourced from the adjusted QuANTUM-First population were used for quizartinib and SC arm in the model to inform the transition from HSCT 1L to post-HSCT 1L relapse. It was assumed that the midostaurin treatment effect would be the same as SC since midostaurin maintenance is not licensed or recommended post-HSCT. These values are summarised in Table 51.

Within the 13 tunnel states for HSCT 2L, comprising one year, only transitions to death were allowed in the model, relapse was not permitted (as a simplifying assumption). The probability of disease-related death was not affected by the treatment received. Data to inform the TPs for the HSCT 2L tunnel states were derived from Styczynski et al, 2019 (25) with the transitions detailed in Table 50. Styczynski et al. 2019 is a retrospective, observational study that investigated death after HSCT in patients with AML, acute lymphoblastic leukaemia (ALL) or chronic myeloid leukaemia (CML). The TPs were derived with the formula described below:

$$Transition\ probability = \frac{Deaths\ in\ X\ days}{Number\ of\ patients\ alive\ at\ the\ beginning\ of\ the\ period}\ x\ \frac{Cycle\ length}{X}$$

Where, X is the duration of the period in days.

Table 50. HSCT 2L transition probability of disease related death, per cycle

Transition from	Transition probability, %	Reference
HSCT 2L, tunnel state 1	3.7	Styczynski et al, 2019 Cohort 2, Figure 1a 2,797 deaths out of 7,1494 patients over 30 days
HSCT 2L, tunnel states 2-3	4.2	Styczynski et al, 2019 Cohort 2, Figure 1b 6,403 deaths out of 61,220 patients over 70 (100-30) days
HSCT 2L recovery, tunnel states 1-10	2.4	Styczynski et al, 2019 Cohort 2, Figure 1c 13,449 deaths out of 58,609 patients, over 265 (365-100) days

Transition from	Transition probability, %	Reference
Post-HSCT 2L recovery	0.4	Styczynski et al, 2019 Cohort 2, Figure 1d 7,527 deaths out of 37,487 patients, over four years (1,460 days)

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplant.
Reference: Styczynski et al. 2019 (25)

The transition of post-HSCT 2L relapse, was assumed to be 50% higher compared with 1L TP, based on clinical expert opinion (12). Given that in 2L no patients in any of the arms received post-HSCT *FLT3* maintenance treatment, it was also assumed that TPs from 2L post-HSCT maintenance to 2L post-HSCT relapse were not affected by treatment choice and were equal to that of the SC arm. These values are summarised in Table 51 as well.

Table 51. Transition probabilities from HSCT to post HSCT relapse, 1L and 2L, by treatment arm

Transition from:	Transition to:	Transition probability, %					
		Quizartinib regimen		SC regimen		Midostaurin regimen	
		Inputs	Reference	Inputs	Reference	Inputs	Reference
Allo-HSCT 1L	1L post-HSCT relapse	[redacted]	QuANTUM-First trial data, quizartinib arm. Assuming time-invariant transitions, [redacted] of [redacted] patients who had HSCT relapsed over an average length of [redacted] days	[redacted]	QuANTUM-First trial data, placebo arm. Assuming time-invariant transitions, [redacted] of [redacted] patients transitioned to HSCT over an average length of [redacted] days	[redacted]	Assumed equal to SC
2L post-HSCT maintenance	2L post-HSCT relapse (Relapse 2)	[redacted]	Assumed equal to SC given quizartinib is not provided in maintenance in 2L	[redacted]	Assumed 50% higher than 1L based on clinical expert opinion	[redacted]	Assumed equal to SC given midostaurin is not provided in maintenance in 2L

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; SC, standard chemotherapy; 1L, first-line treatment; 2L, second-line treatment.
Reference: Daiichi Sankyo, 2022 (98)

B.3.3.2.4 Transitions from relapse

TPs from the Relapse1 and Post HSCT relapse 1L to Death for the quizartinib and SC regimens were derived from respective arms of the QuANTUM-First trial using the ITT population. Transition from these health states to death were treatment specific to account for differences in OS since this was not prevalent in the transition from CR1 to death. The probability of transition from Relapse1 to death used survival data censored for relapse so considered only deaths which preceded relapse or occurred in the same 28-day cycle.

Time-invariant TP from the Relapse1 to Death were based on subjects who achieved CRc but later relapsed, and who did not undergo any type of transplantation (regardless of whether it was protocol-specified or not) during the study and died in QuANTUM-First trial. Due to the lack of data to inform this TP in the RATIFY trial, it was assumed that the TP for midostaurin would be the same as that for the quizartinib. This is considered a conservative assumption, assuming all FLT3i treatments have the same efficacy for patients who relapsed.

Time-invariant TP from the Post -HSCT relapse 1L to Death were based on subjects in the QuANTUM-First ITT set who achieved CRc but later relapsed, but considered only those who underwent protocol-specified HSCT and died. As this data is not available in the RATIFY trial, it was assumed that this TP for midostaurin would be the same as that for the SC (placebo) arm, since no midostaurin maintenance is given in the midostaurin regimen post-HSCT.

Information to derive TPs from the Relapse1 to CR2 health state was not available in the QuANTUM-First trial nor in the RATIFY trial which enrolled newly diagnosed patients and had limited follow up time to evaluate outcomes in the next treatment line. As such, these data were sourced from the literature, namely publications on the ADMIRAL trial, which explored the efficacy of gilteritinib for refractory or relapsed AML patients with a *FLT3* mutation, therefore capturing the effect of 2L treatment regimens (118, 119). Since 2L regimens in the model included gilteritinib and FLAG-Ida (fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor) (section B.3.5.1.2), the TPs were derived from pooled data from the ADMIRAL trial (i.e. including patients who received gilteritinib and FLAG-Ida). Data from the ADMIRAL

trial was adjusted for a 28-day cycle length. The same TPs for these transitions were applied for all comparators (i.e. 2L treatment were assumed to have the same efficacy regardless of whether the patients received the quizartinib, midostaurin or SC regimen in 1L). This was considered a reasonable assumption as in a subgroup analysis of ADMIRAL the HR for death in patients that did and did not receive a FLT3i treatment in 1L was similar.

Regarding the transition from the Relapse2 to Death, it was assumed to be the same as the transition probability from the Relapse1 to Death, based on clinical expert opinion.

The transitions from the Relapse 1, Post HSCT relapse 1L, and Relapse 2 health states are summarised in Table 52.

Table 52. Transition probabilities from Relapse 1, Post HSCT relapse 1L, and Relapse 2 by treatment arm

Transition from:	Transition to:	Transition probability, %					
		Quizartinib regimen		SC regimen		Midostaurin regimen	
		Inputs	Reference	Inputs	Reference	Inputs	Reference
Relapse 1	Relapse 1	Residual	Residual	Residual	Residual	Residual	Residual
	CR2	30.0	ADMIRAL trial (Perl et al., 2019) 120 (gilteritinib n=103 and salvage chemotherapy n=17) patients of 225 patients (gilteritinib N=149 and salvage chemotherapy N=76) responding over 1.96 months (weighted average time to CRc in gilteritinib arm [2.3 months, N of Relapse before enrollment=149] and in salvage chemotherapy arm [1.3 months, N=76]))	30.0	The transition probability from Relapse 1 to CR2 was assumed to be the same for all regimens	30.0	The transition probability from Relapse 1 to CR2 was assumed to be the same for all regimens
	Death	[redacted]	DSE Q-F DOF, 2023. Out of [redacted] subjects who achieved CRc but later relapsed, and who did not undergo any type of transplantation during the study, [redacted] died, with a mean follow-up time of [redacted] months in quizartinib arm	[redacted]	DSE Q-F DOF, 2023. Out of [redacted] subjects who achieved CRc but later relapsed, and who did not undergo any type of transplantation during the study, [redacted] died, with a mean follow-up time of [redacted] months in SC (placebo) arm	[redacted]	The transition probability was assumed to be the same as that for the quizartinib arm
Post HSCT relapse 1L	Post HSCT relapse 1L	Residual	Residual	Residual	Residual	Residual	Residual
	Death	[redacted]	DSE Q-F DOF, 2023. Out of [redacted] subjects who achieved CRc but later relapsed, and who underwent protocol-specified HSCT during the course of the study, [redacted] died, with a mean follow-up time of [redacted] months in quizartinib arm	[redacted]	DSE Q-F DOF, 2023. Out of [redacted] subjects who achieved CRc but later relapsed, and who underwent protocol-specified HSCT during the course of the study, [redacted] died, with a mean follow-up time of [redacted] months in SC (placebo) arm	[redacted]	The transition probability was assumed to be the same as that for the SC (placebo) arm

Transition from:	Transition to:	Transition probability, %					
		Quizartinib regimen		SC regimen		Midostaurin regimen	
		Inputs	Reference	Inputs	Reference	Inputs	Reference
Relapse 2	Relapse 2	Residual	Residual	Residual	Residual	Residual	Residual
	Death	[redacted]	Assumed the same as the transition probability from Relapse 1L to Death based on the clinical expert opinion	[redacted]	Assumption, same efficacy inputs for all interventions	[redacted]	Assumption, same efficacy inputs for all interventions

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; CRh, complete remission with partial hematologic recovery; CR1, first CR; CR2, second CR; DSE Q-F DOF, Daiichi Sankyo Europe QuANTUM-First data on file HSCT, haematopoietic stem cell transplantation; Relapse 1, first relapse; Relapse 2, second relapse; SC, standard chemotherapy; 1L, first-line treatment; 2L, second-line treatment.
Reference: Perl, 2019 (118)

B.3.3.2.5 Transitions from refractory and CR2

As described in section B.3.3.2.4, transitions from relapse data for subsequent treatment is not available in either the QuANTUM-First or RATIFY trials. Therefore, the data to inform the TPs from the Refractory and CR2 health states were derived from pooled data from the ADMIRAL trial (118, 119). The same TPs for these transitions were applied for all comparators and adjusted for a 28-day cycle length.

In 2L management of AML, although not as common, HSCT plays an important role in treatment goals (120). HSCT is the only curative therapy for patients with primary refractory disease and offers the best chance for cure in those who relapse after initial chemotherapy (8). As a result, patients refractory to 1L treatment but achieving complete remission with gilteritinib are eligible for transplant. However, patients who received HSCT in 1L treatment were not able to receive HSCT in 2L in the model. This was in line with clinical expert opinion which advised that a negligible proportion of patients would receive a second HSCT (12).

The TP values from the refractory and CR2 health states are summarised in Table 53.

Table 53. Transition probabilities from Refractory, Relapse1, CR2 and Relapse2, by treatment arm

Transition from[a]:	Transition to:	Transition probability, %	Reference[b]
Refractory	Refractory	Residual	Residual
	CR2	14.3	ADMIRAL trial (Perl et al., 2019) 41 (31 patients received gilteritinib and 10 received salvage chemo) of 146 patients (98 from gilteritinib arm and 48 from salvage chemotherapy arm) with primary refractory AML achieved a CR/CRh responding over 1.97 months (weighted average time to CRc in gilteritinib arm [2.3 months, N of primary refractory disease without HSCT before enrollment=98] and in salvage chemotherapy arm [1.3 months, N=48]))
	Death	5.2	ADMIRAL trial (Perl et al., 2019) 60-day mortality weighted by trial arm (60-day mortality rate = 7.7% in gilteritinib arm [n=247] and 19.0% in salvage chemotherapy arm [n=124]), assumed to be time-invariant and adjusted to transition probability for 28-day cycle length
CR2	CR2	Residual	Residual
	Relapse 2	2.2	ADMIRAL follow up (Perl et al., 2022). The 2-year cumulative relapse rate in gilteritinib treated patients who achieved a best response of CR was 56.2%[c]
	HSCT 2L	12.5	ADMIRAL follow up (Perl et al., 2022). 355 patients (246 patients received gilteritinib and 109 received salvage chemotherapy) were included in the safety analysis set. 83 (64 from gilteritinib arm and 19 from salvage chemotherapy arm) underwent HSCT (23.4%), with the median follow-up of 37.1 months
	Death	2.8	ADMIRAL follow up (Perl et al., 2022). One year mortality weighted by trial arm (62.1% in gilteritinib arm [n=247] and 83.2% in salvage chemotherapy arm [n=124]), assumed to be time-invariant and adjusted to 28-day cycle length

Abbreviations: CR, complete remission; CRh, complete remission with partial hematologic recovery; CR1, first CR; CR2, second CR; HSCT, haematopoietic stem cell transplantation; Relapse1, first relapse; Relapse2, second relapse; SC, standard chemotherapy; 1L, first-line treatment; 2L, second-line treatment.
Reference: Perl, 2019 (118)
Notes: a. It is assumed that TPs across treatment arms will be the same for 2L health states b. Data from the total trial population (i.e. including those that received either salvage chemotherapy or gilteritinib was used to inform the TPs c. A meaningful assessment of cumulative relapse rates in the SC arm could not be performed because bone marrow samples were only collected up to the end of treatment, and nearly all patients in the SC arm had discontinued treatment after ≤2 treatment cycles

B.3.3.3 Time-varying transition probabilities

CEM uses the following time-varying data from the adjusted QuANTUM-First population group to inform the transition:

- From CR1 to Relapse1: Relapse from CRc, censored at the start date of all HSCT
- From CR1 to Death: Death from CRc, censored at the start date of all HSCT and relapse
- From HSCT 1L to Death: Death from protocol-specified HSCT, censored at relapse

These time-varying data were extrapolated beyond the time horizon of the trial through survival modelling. The “flexsurv” package in R was used to fit the seven standard parametric models, exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal and Weibull as described in NICE DSU TSD 14, to the trial data (121).

The CEM utilized extrapolations for the quizartinib arm, which served as the reference arm while the remaining comparators (SC and midostaurin) were estimated using the comparative efficacy inputs from the MAIC. Survival curves were fitted to only the adjusted population (subset of ITT under 60 years of age matched the RATIFY *FLT3-ITD+* population). The results of the survival analysis for the adjusted population are detailed in the subsequent sections. To conduct scenarios using QuANTUM-First data alone and the outputs from the ML-NMR, the full QuANTUM-First population was used. These analyses are presented in Appendix M.

Assessing the suitability of survival curves is essential to ensuring that the curve adequately reflects the underlying data and expected long-term survival. In this case, the adoption of a cure model with a cure-point within the trial follow-up period places more emphasis on close fit during the trial follow up than long-term plausibility. Following the systematic survival model selection process recommended by NICE DSU TSD14 (121) a range of methods, when appropriate, have been used to assess the suitability of parametric survival models:

- Log-cumulative hazard plot and Schoenfeld residual test: It is crucial to examine the hazard rates observed over time when selecting appropriate parametric

models, as different models incorporate varying hazard functions. Log-cumulative hazard plots can be constructed to illustrate the hazards observed in a clinical trial (121). These allow an inspection of whether hazards are likely to be non-monotonic. monotonic or constant. In addition, these plots allow an assessment of whether the PH assumption, which underpins the PH modelling technique, is reasonable.

- Visual inspection: this involves visually evaluating how well a parametric survival model fits the observed KM data. The parametric survival model that most closely follows the observed KM curve would be considered to have the best fit.
- Akaike information criterion (AIC) and Bayesian information criterion (BIC) tests: The AIC and the BIC provide useful statistical tests of the relative fit of parametric survival models (121). The AIC and BIC statistics weigh up the improved fit of models with the potentially inefficient use of additional parameters (some parametric models have more parameters than others). Lower AIC and BIC values indicate better (complexity adjusted) goodness-of-fit to the data (121).

B.3.3.3.1 Relapse from CRc, censored at the start date of all HSCT

IPD from the QuANTUM-First trial (under 60 population) was used to derive the relapse from CRc curve for quizartinib and SC. Since the SC curve was not used in the base case analyses, model selection is only discussed for the quizartinib curve.

In the QuANTUM-First trial, RFS was defined as the time from randomisation, for patients who achieved CRc during induction, until the date of documented relapse or death from any cause, whichever occurred first. However, as these curves in model are used to inform the transition from CR1 to Relapse1 health state, they are referred to as ‘relapse from CRc’ curves rather than RFS curves. In addition, to account for competing risks, patients that died or began receiving HSCT were censored. Individuals receiving HSCT were censored at the start date of the conditioning regimen.

Figure 22 presents the KM curves for relapse from CRc for SC and quizartinib.

Figure 22. KM curves for relapse after CRc

Schoenfeld residuals and log-cumulative hazard plot

Figure 23 and Figure 24 present the Schoenfeld residuals and log-cumulative hazard plot for relapse from CRc respectively. The curves crossed only at the beginning of the trial and the hazard for quizartinib remains below SC for the remainder of the time horizon. Based on this, it was assumed that although the conditions for the proportional hazard assumption (PHA) were not fully satisfied, it is acceptable to consider proportional hazards, especially in the context of functional cure.

Figure 23. Schoenfeld residuals plot for relapse from CRc

Abbreviations: CRc, composite complete remission.

Figure 24. Log-cumulative hazard plot for relapse from CRc

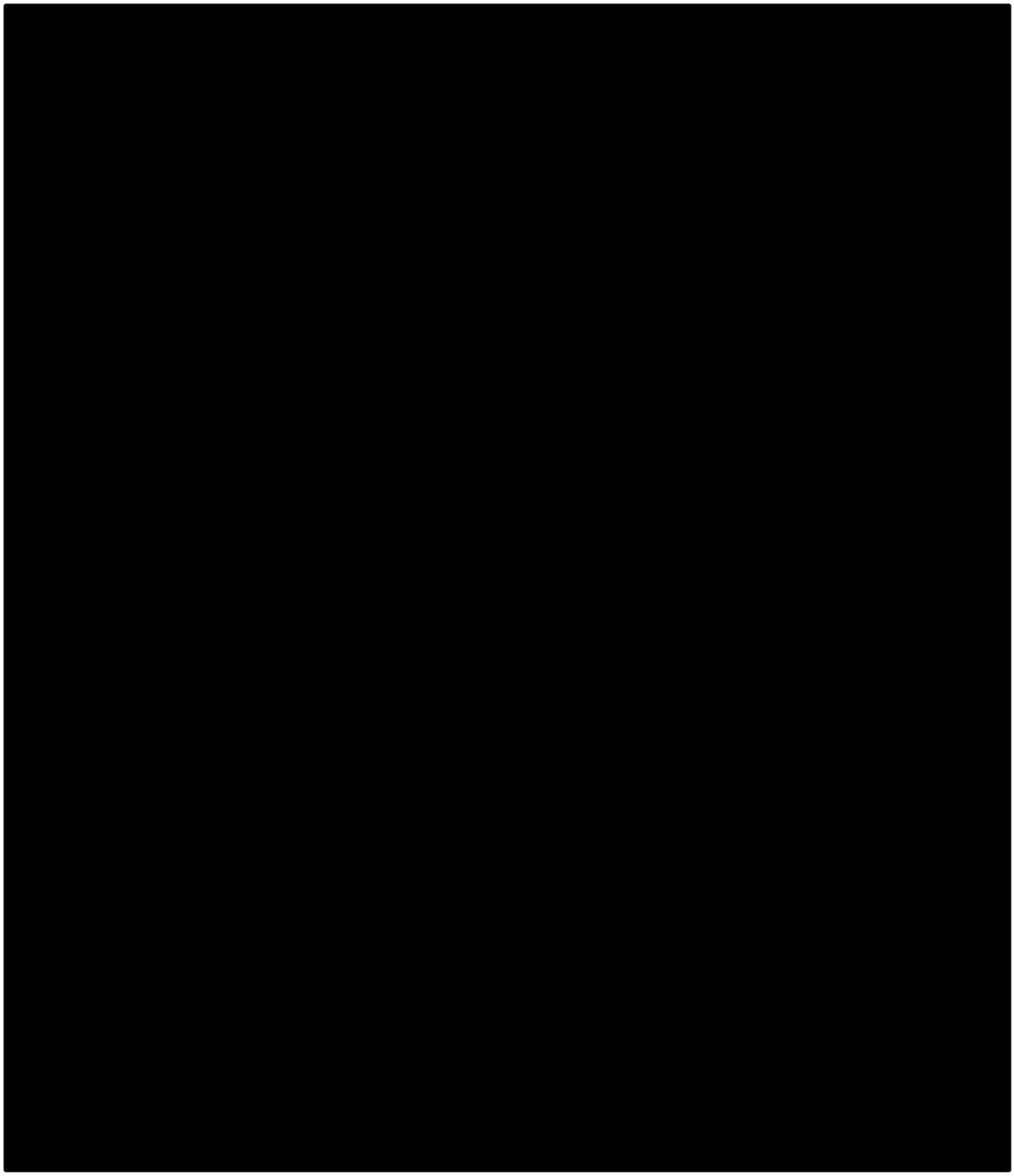
Abbreviations: CRc, composite complete remission.
Notes: placebo refers to the SC arm.

Visual inspection

To conform with the analyses base case (i.e., using quizartinib as a reference curve and MAIC outputs for the remaining comparators), seven parametric models were fitted separately to quizartinib and SC relapse from CRc data. There were no convergence issues in the fitting process.

Figure 25 and Figure 26 present the visual fit of independent models to the data in the quizartinib and SC arms. In the quizartinib arm, generalized gamma, Gompertz, and log-normal fit satisfactorily to the observed smoothed hazard curve, however, most models failed to capture the declining trajectory of the curve toward the end of the observed data.

Figure 25. Independent models for relapse from CRc (10-year)



Abbreviations: CRc, composite complete remission; KM, Kaplan Meier.

Figure 26. Smoothed hazard curves (relapse from CRc)

AIC and BIC test

Table 54 presents the AIC and BIC scores for the independent models in quizartinib arm. AIC and BIC scores were lowest for the exponential fit for quizartinib arm but the close scoring alternative had a more acceptable visual fit. Hence, log-normal appears to be the best overall fitting curve for the quizartinib arm with log-logistic, gamma and Weibull being close alternatives.

Table 54. AIC and BIC scores for independent models of relapse from CRc in the quizartinib arm

Distribution	AIC	BIC
Exponential	294.8	297.5
Gamma	296.7	302.3
Generalized gamma	297.6	306.0
Gompertz	296.2	301.8
Log-logistic	296.2	301.7
Log-normal	295.6	301.2
Weibull	296.7	302.3

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CRc, composite complete remission; SC, standard chemotherapy.

Comparative efficacy

To obtain the comparative efficacy of quizartinib vs midostaurin and SC, data from the MAIC (see Section B.2.8) was used in the model (Table 55). The CIR HR from the MAIC was used to inform the relative efficacy of midostaurin and SC, where the quizartinib arm was selected as the reference arm.

As described in Section B.3.3.2.1, the relapse after CR data was employed in the MAIC, and the relapse after CRc (i.e., CR + CRi) was modelled. The underlying assumption is that the relative treatment effect in relapse of midostaurin (vs quizartinib) was the same for CR and CRc.

Given that post-hoc analysis of CRi patients in QuANTUM-First showed many were CR by the first day of consolidation, and the majority proceeded to receive consolidation treatment or HSCT, it is reasonable to consider that CRi patients would have the same or similar prognosis as CR patients in QuANTUM-First study. This seems to be the most reasonable position given that evidence to determine the CRc rate in RATIFY is lacking, and the utilization of the CR criteria in the model does not algin with clinical practice. It was deemed a conservative approach in the MAIC as it underestimates quizartinib's efficacy by excluding CRi patients from the analysis.

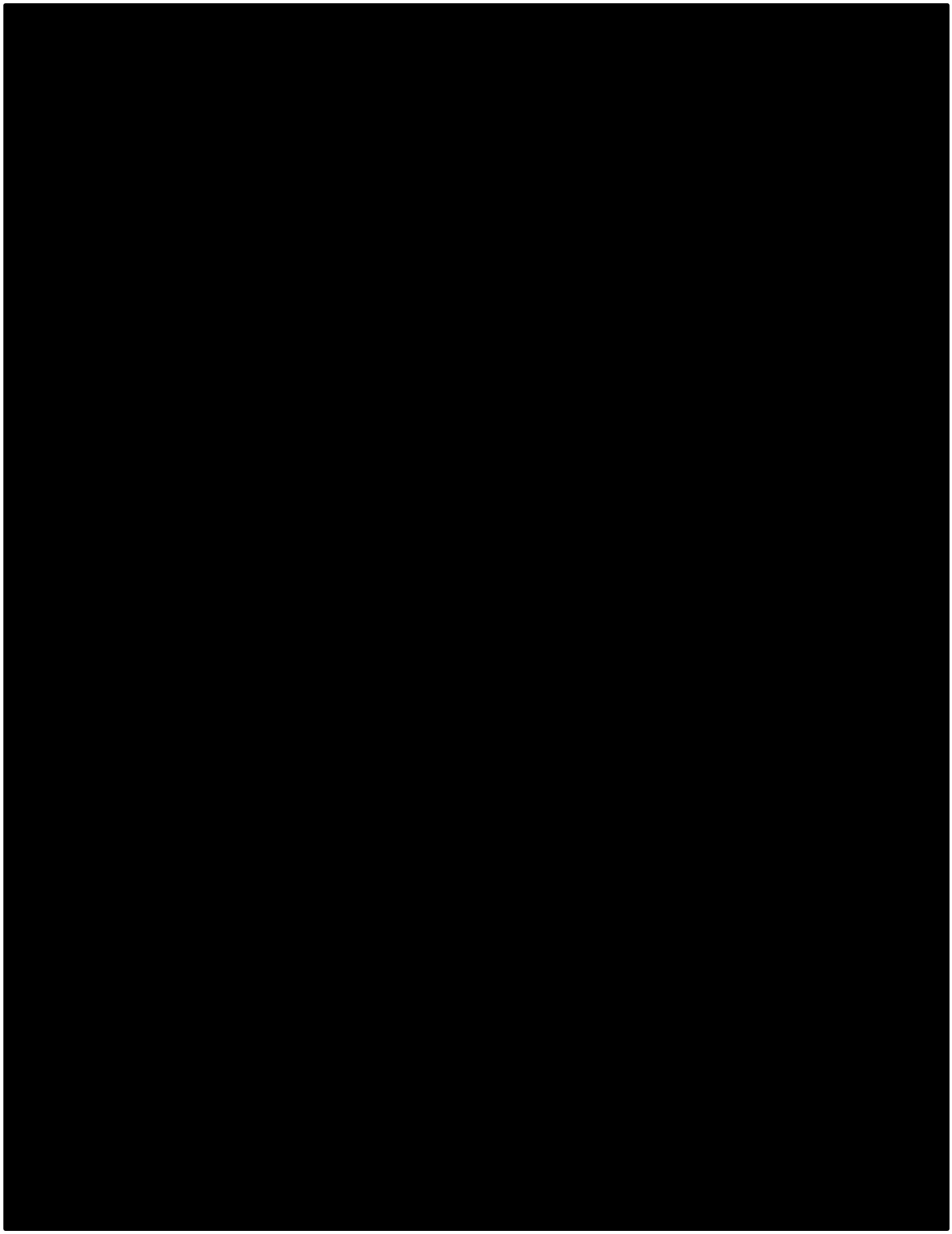
Table 55. Comparative efficacy: MAIC CIR HRs to inform relapse from CRc

	HR	SE	95% lower CI	95% upper CI	Reference
Quizartinib vs midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	MAIC
Quizartinib vs SC	[redacted]	[redacted]	[redacted]	[redacted]	MAIC

Abbreviations: CI, confidence interval; CIR, cumulative incidence of relapse; CRc, composite complete remission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; SC, standard chemotherapy; SE, standard error.

The 3-year and 10-year projected relapse from CRc, before considering the cure assumption, are presented in Figure 27. The final curves used in the base case are presented in section B.3.3.4.

Figure 27. Relapse from CRc 3-year and 10-year projection in model base case, quizartinib, SC, and midostaurin arm



Abbreviations: CRc, composite complete remission; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; SC, standard chemotherapy.

B.3.3.3.2 Death from CRc, censored at the start date of all HSCT and relapse

IPD from the QuANTUM-First trial (under 60 population) was used to derive death from CRc data for quizartinib and SC. As for the relapse endpoint, the SC IPD was not used in the base case analyses, therefore parametric model selection is only discussed for the quizartinib curve.

The death from CRc endpoint presented for patients in first CRc, which is defined as the time between the date patients enter first CRc and the date of death due to any cause. Patients who relapse or receive HSCT are censored, and patients who did not progress, die, or receive HSCT are censored on the last known date alive.

Figure 28 presents the KM data for survival after CRc.

Figure 28. KM curves for death from CRc

Abbreviations: CRc, composite complete remission; KM, Kaplan Meier.

Schoenfeld residuals and log-cumulative hazard plot

Figure 29 and Figure 30 present the Schoenfeld residuals and log-cumulative hazard plot for death from CRc respectively. Schoenfeld residual plots were not informative, but log-cumulative hazard plots showed crossing of the curves at two points indicating that the PHA is violated. Nevertheless, the base case analyses assume PHA for this endpoint to allow a direct comparison between quizartinib, SC and midostaurin. Scenario analyses show that the treatment effect assumed for survival after CRc has a limited impact on the results.

Figure 29. Schoenfeld residuals plot for death from CRc

Abbreviations: CRc, composite complete remission

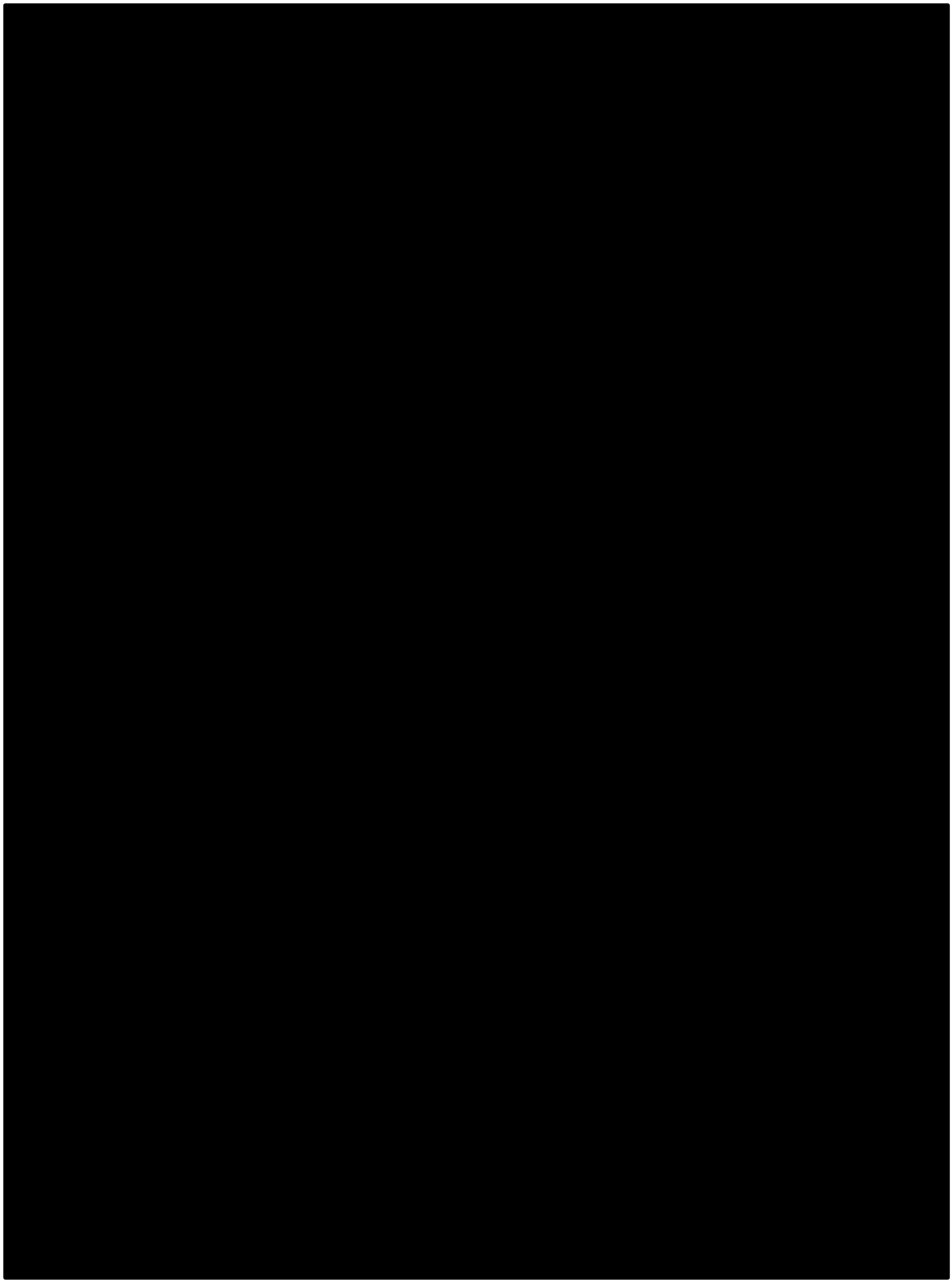
Figure 30. Log-cumulative hazard plot for death from CRc

Abbreviations: CRc, composite complete remission
Notes: placebo refers to the SC arm.

Visual inspection

As before, seven parametric models were fitted separately to quizartinib and SC death from CRc data. The Gompertz model did not converge. Figure 31and Figure 32 present the model fits and smoothed hazard curves, respectively. For the quizartinib arm, generalized gamma and exponential models had poor visual fit. All models except the Gompertz and exponential gave good fits to the observed smoothed hazard curve.

Figure 31. Independent models for death from CRc (10-year)



Abbreviations: CRc, composite complete remission; KM, Kaplan Meier.

Figure 32. Smoothed hazard curves for death from CRc

AIC and BIC test

Table 56 presents the AIC and BIC scores for the independent models in both the quizartinib arm. In the quizartinib arm, log-normal had the lowest AIC score but other curves had comparable AIC. In terms of BIC, the exponential had the lowest score followed by log-normal. Based on visual fit, log-normal appears to be the best fitting distribution with log-logistic, gamma and Weibull distributions being acceptable alternative fits.

Table 56. AIC and BIC scores for independent models of death from CRc in the quizartinib arm

Distribution	Quizartinib	
	AIC	BIC
Exponential	121.6	124.4
Gamma	121.7	127.3
Generalized gamma	122.5	130.9
Gompertz	-	-
Log-logistic	121.7	127.3
Log-normal	121.4	127.0
Weibull	121.7	127.3

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CRc, composite complete remission; SC, standard chemotherapy.

Comparative efficacy

To obtain the comparative efficacy of midostaurin, the data from the MAIC (as described in section B.2.8) was used in the model. The quizartinib arm was selected as the reference treatment arm.

Based on the model structure provide in the section B.3.2.2, inputs of survival after CRc are required for all regimens. However, the survival after CRc was not available in the RATIFY trial. Consequently, the OS (i.e., survival from randomization) was utilized in the MAIC. Therefore, HR from randomization is employed in the model as a proxy for HR from CRc, which was applied to the reference curve (i.e. survival after CRc for the quizartinib arm), to ascertain the efficacy for midostaurin and SC. The underlying assumption is that the relative treatment effect in survival of midostaurin (versus quizartinib) was the same from randomization and from CRc. Given the lack of data to estimate the relative treatment effect for survival after CRc, this is the best available measure of relative treatment effect between quizartinib and midostaurin. To understand the validity of the assumption, we evaluated post hoc the treatment effect between placebo and quizartinib on survival from randomization (i.e., OS) and survival from CRc (i.e., endpoint used in the model). Trial data shows that the quizartinib treatment effect (vs placebo) is higher when looking at survival after CRc (HR = [redacted]) (116), comparing with survival from randomisation (HR = 0.780) (76). Based on this finding, it was deemed reasonable to assume the same treatment effect between quizartinib and midostaurin for survival from CRc and randomisation. As mentioned before, scenario analyses were conducted (section B.3.9.3), where no differences in survival after CRc are assumed.

Table 57. Comparative efficacy: MAIC OS HRs to inform death from CRc

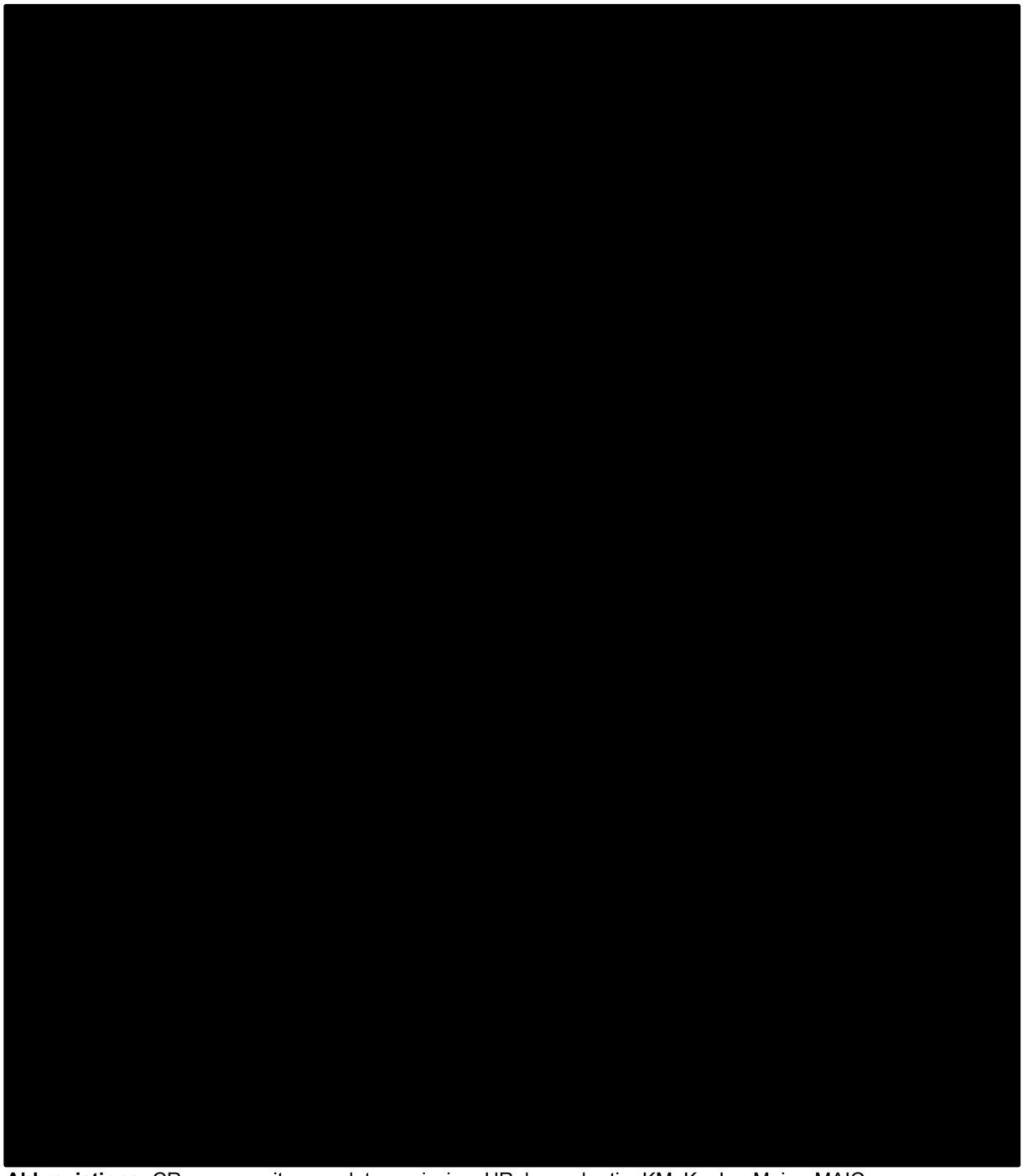
	HR	SE	95% lower CI	95% upper CI	Reference
Quizartinib vs midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	MAIC
Quizartinib vs SC	[redacted]	[redacted]	[redacted]	[redacted]	MAIC

Abbreviations: CI, confidence interval; CRc, composite complete remission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; SC, standard chemotherapy SE, standard error.

Based on these results, the death from CRc curve extrapolated by log-normal distribution was used in the base case for quizartinib. The HRs derived from the MAIC were used to obtain the curves for SC and midostaurin.

The 3-year and 10-year projected survival from CRc, before considering the cure assumption, are presented in Figure 33. The final curves used in the base case are presented in section B.3.3.4.

Figure 33. Death from CRc 3-year and 10-year projection in model base case, quizartinib, SC, and midostaurin arm



Abbreviations: CRc, composite complete remission; HR, hazard ratio; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; SC, standard chemotherapy.
Notes: placebo refers to the SC arm.

B.3.3.3.3 Death from protocol-specified HSCT 1L, censored at relapse

QuANTUM-First trial data (under 60 population) for patients who received protocol-specified HSCT was used to model survival post-HSCT. Patients who relapsed were censored at the date of relapse. Those patients who were lost to follow-up, or alive at the end of follow-up period were censored at last known date alive.

Independent curves were used in the model to estimate survival after HSCT for quizartinib and SC.

Figure 34 presents the KM data for survival after HSCT.

Figure 34. KM curves for death from HSCT

Schoenfeld residuals and log-cumulative hazard plot

Figure 35 and Figure 36 present the Schoenfeld residuals plot and log-cumulative hazard plot for death from HSCT respectively. The Schoenfeld residuals plot showed no clear pattern over time and the log-cumulative hazard plots did not show any crossing of the curves. This suggested that the PHA holds. However, since there are no estimates of relative treatment effect on survival after HSCT from the ITCs, independent parametric models were used for quizartinib and SC.

Figure 35. Schoenfeld residuals plot for death from HSCT

Abbreviations: HSCT: allogeneic stem cell transplantation

Figure 36. Log-cumulative hazard plot for death from HSCT

Abbreviations: HSCT: allogeneic stem cell transplantation
Note: Placebo refers to SC treatment arm

Visual inspection

As for the previous data, seven models were fit as independent models to the death from HSCT data. There were no convergence issues across the models in either treatment arm.

Figure 37 present the visual model extrapolations in the SC and quizartinib arms. In the SC arm, the exponential model estimated the least survival while Gompertz estimated the highest survival. All other curves look plausible when compared to the observed KM curve. In respect to quizartinib, the exponential curve estimates the poorest survival over time while Gompertz estimates the highest survival. However, based on visual fit, considering the plateau in hazard, Gompertz appears to be fitting the observed data the best.

Figure 38 presents the smoothed hazard curves of post-HSCT OS in the SC and quizartinib arms. Generalized gamma had the best fit while exponential had the worst fit to observed hazards in both the arms.

Figure 37. Independent models for death from HSCT in the quizartinib arm

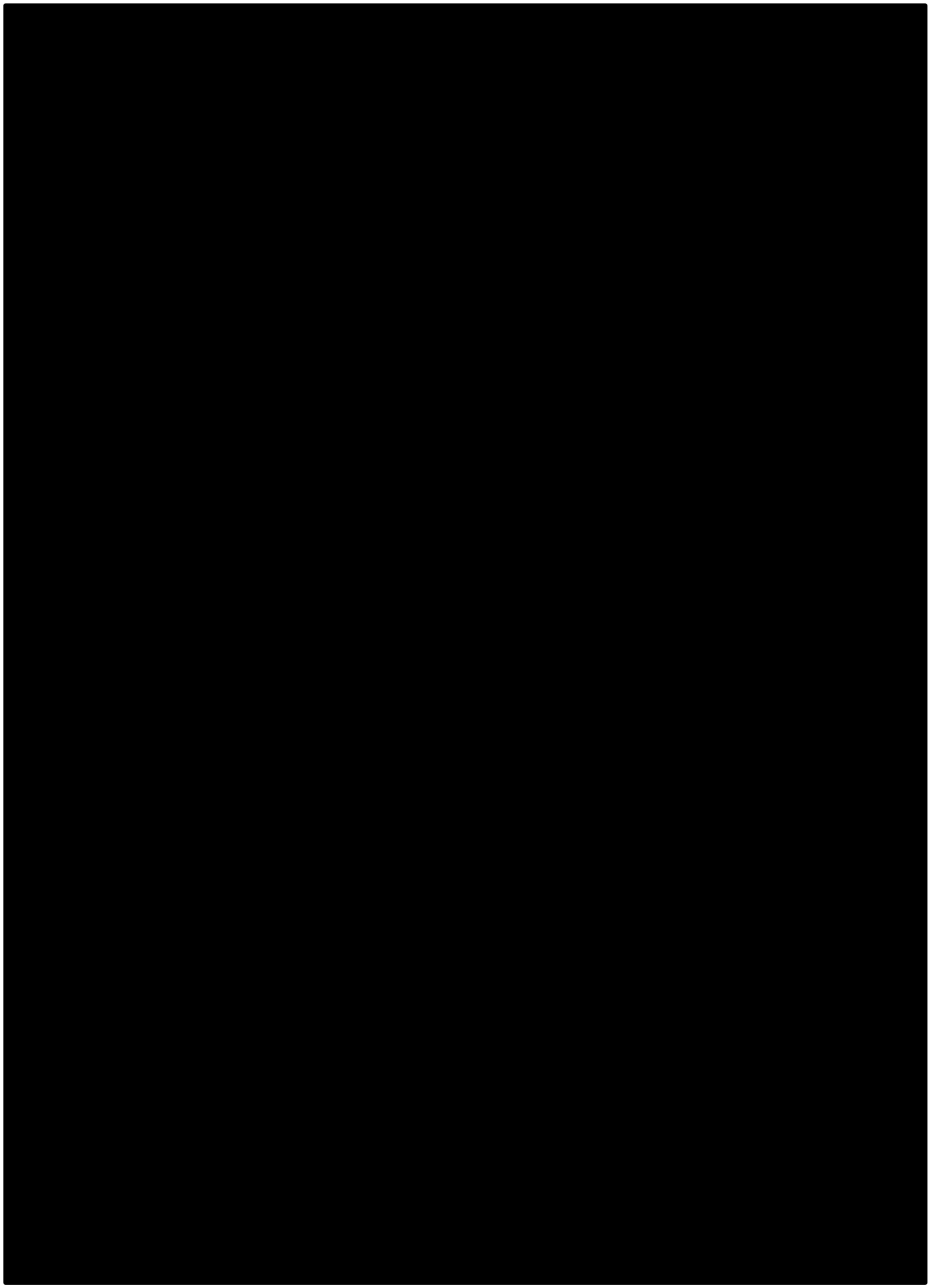


Figure 38. Smoothed hazard curves for death from HSCT

AIC and BIC test

Table 58 presents the AIC and BIC scores for the independent models of post-HSCT OS in the SC and quizartinib arms. Ignoring the least AIC and BIC in the SC arm due to poos visual fit, generalized gamma had the best statistical fit followed by log-normal with the former having better visual fit. Generalized gamma is the best fitting curve for the SC arm. In the quizartinib arm, the Gompertz distribution had the least AIC and BIC with log-normal having the next best statistical fit. When considered together with the visual fit, Gompertz distribution is the best fitting for quizartinib arm with log-normal being a good second choice.

Table 58. AIC and BIC scores for independent models of death from HSCT in the quizartinib arms

Distribution	Quizartinib		SC	
	AIC	BIC	AIC	BIC
Exponential	149.0	151.2	154.7	156.7
Gamma	147.0	151.5	151.5	155.5
Generalized gamma	146.0	152.7	148.4	154.4
Gompertz	142.9	147.4	140.6	144.6

Distribution	Quizartinib		SC	
	AIC	BIC	AIC	BIC
Log-logistic	146.7	151.2	150.9	154.9
Log-normal	145.9	150.3	149.8	153.8
Weibull	146.8	151.3	151.2	155.2

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; AIC, Akaike Information Criterion; BIC: Bayesian Information Criterion.

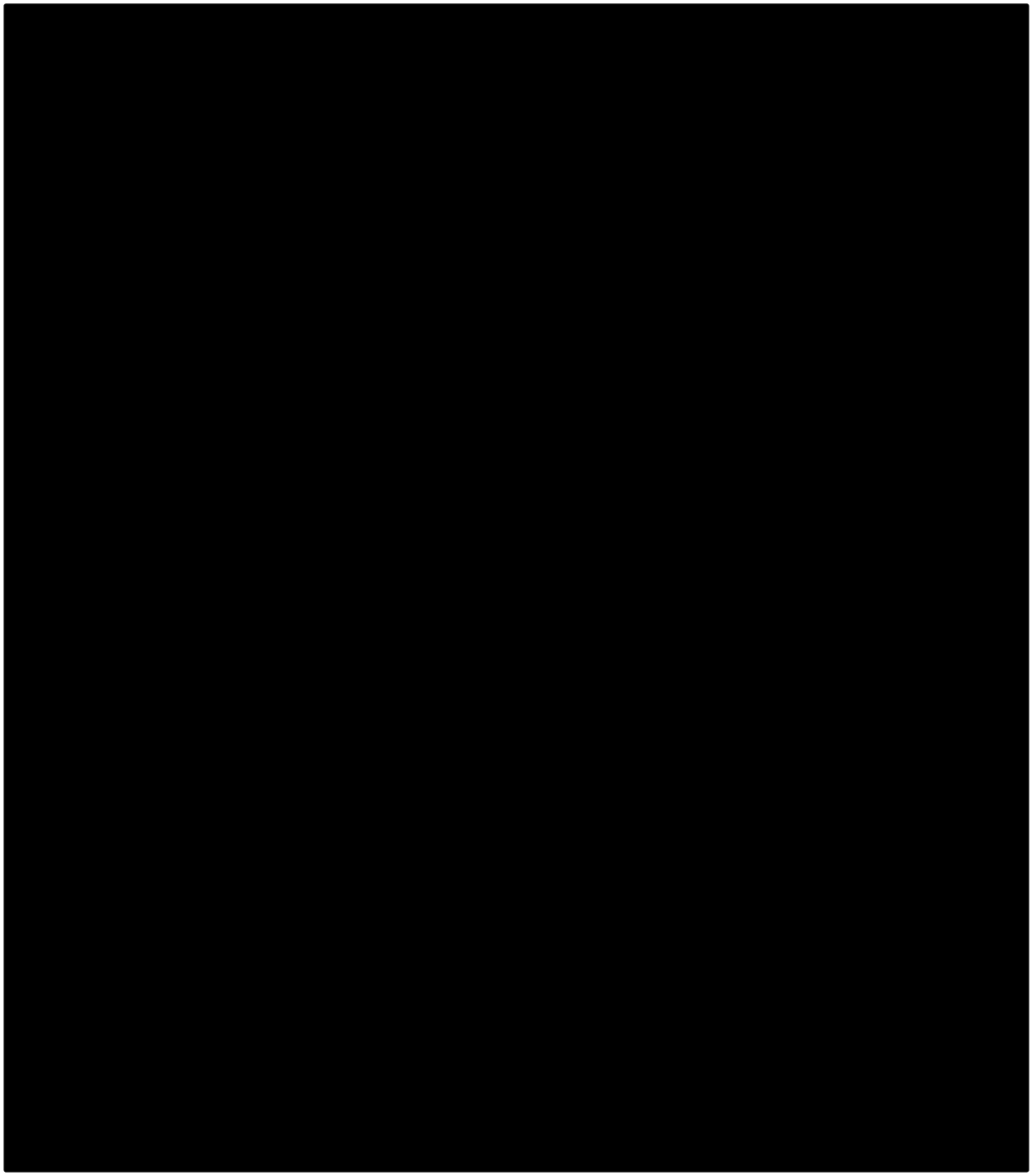
Comparative efficacy

As mentioned before, independent models were used for quizartinib and SC.

Given the lack of data to estimate the relative treatment effect for survival after HSCT between quizartinib and midostaurin, for the base case analyses it was assumed that midostaurin survival post HSCT was equivalent to the SC arm of the QuANTUM-First trial. This assumption was made since patients in the RATIFY trial (and clinical practice) are not allowed to receive maintenance treatment post-transplant. In turn, the quizartinib data reflects a proportion of patients that received maintenance treatment after transplant (with costs also considered in the base case analyses). To address the model sensitivity to this assumption, a scenario analyses was conducted where the survival post-transplant is set equal to the quizartinib arm.

The 3-year and 10-year projected survival from HSCT, before considering the cure assumption, are presented in Figure 39. The final curves used in the base case are presented in section B.3.3.4.

Figure 39. Death from protocol-specified HSCT 3-year and 10-year projection in model base case, quizartinib, SC, and midostaurin arm



B.3.3.3.4 Summary of survival model selection in the base case

A log-normal model was identified as the most suitable survival curve for relapse from CRc and death from CRc outcomes for the quizartinib arm to use in the base case.

These two curves were used as the reference curve, with the HRs from the MAIC to estimate the relapse from CRc and death from CRc outcomes for SC and midostaurin.

For survival after HSCT, independent models for quizartinib and SC are used. The base case analyses assumes that the survival after HSCT for midostaurin is the same as observed in the SC arm. Gompertz and generalised gamma parametric models were used for quizartinib and SC, respectively.

Table 59 provides a summary of the models selected for the base case analyses.

Table 59. Model selection summary table

Endpoint	Treatment Arm	Model	Parameters
Relapse from CRc	Quizartinib (reference arm)	Log-normal	[redacted]
Death from CRc	Quizartinib (reference arm)	Log-normal	[redacted]
Death from protocol-specified HSCT	Quizartinib	Gompertz	[redacted]
	SC	Generalized gamma	[redacted]

Abbreviations: CRc, composite complete remission; SD, standard deviation.

B.3.3.3.5 Comparison of adjusted and unadjusted QuANTUM-First population KM curves

As described in the section B.2.8.4, the QuANTUM-First population is adjusted using TEMs in the MAIC analysis for a meaningful survival comparison with midostaurin. This adjusted QuANTUM-First population, a RATIFY-like population, is used in the base case. The comparison of adjusted and unadjusted QuANTUM-First population KM curves, in terms of relapse from CRc, death from CRc, and death from protocol-specified HSCT 1L, are presented in Figure 40, Figure 41, and Figure 42, respectively.

Figure 40. Effect of age adjustment to QuANTUM-First population KM curves in relapse from CRc

Figure 41. Effect of age adjustment to QuANTUM-First population KM curves in death from CRc

Figure 42. Effect of age adjustment to QuANTUM-First population KM curves in death from protocol-specified HSCT 1L

B.3.3.3.6 Time-varying transition probability calculation

The relapse from CRc and death from CRc curves were used to derive time-dependent TPs for CR1 to relapse and CR1 to dead. These were derived from the cumulative hazard function of the parametric distribution, meaning that the TPs change as the time in the model increases. TPs were estimated from hazard rates using Equation 1 (9).

Equation 1. $tp(tu) = 1 - \exp\{H(t-u) - H(t)]$

where tp indicates the TP, tu the cycle for which the TP is estimated, u the cycle length and H(t) the cumulative hazard function of the parametric distribution (9).

For example, the form of the cumulative hazard function for the Weibull distribution is given by Equation 2.

Equation 2. $H(t) = \lambda t^{\gamma}$

with λ being the scale parameter and γ being the shape parameter of the distribution. These are estimated from the regression analysis conducted in R when fitting the Weibull distribution.

Substituting and rearranging the cumulative hazard function in Equation 1 into the general form in Equation 2, results in Equation 3, which can be used to estimate time-dependent TPs.

Equation 3. $tp(tu) = 1 - \exp\{\lambda t(t-u)^{\gamma} - \lambda t^{\gamma}]$

B.3.3.4 Modelling cure

In line with committee's preferred assumptions in previous NICE HTAs in AML, the model was developed to allow modelling 'functional' cure in patients with long term remission (105) (101).

With the cure approach, patients who remain in the CR1 and HSCT 1L health states beyond three years were assumed to be cured. Cure was implemented by setting the probability of relapse from these health states to zero (i.e. RFS was assumed to remain constant until death). A two-fold Standardized Mortality Ratio (SMR) was applied to the general population mortality data to calculate the post-cure mortality. This cure approach is consistent with the methodology used in TA523. Patients who entered the Refractory, Relapse, and Post-HSCT relapse health states were not considered to be curable. Three years was selected as the cure point as this is when the OS curves flattened and was also in line with prior TAs in AML (TA523 and TA642) (103, 104) and clinical expert opinion (12).

After the cure point it was assumed that patients in these health states do not accrue disease management costs and utilities were assumed to be the same as those of the age and gender adjusted general population (HSE, 2014) (122).

The relapse from CRc, death from CRc and death from protocol-specified HSCT 1L curves used in the model after applying cure are presented in Figure 43, Figure 44, and Figure 45, respectively.

Figure 43. Relapse from CRc for adjusted population, censored at the start date of all HSCT, after applying cure

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplant; KM, Kaplan-Meier.
Notes: placebo refers to the SC arm.

Figure 44. Death from CRc for adjusted population, censored at the start date of all HSCT and relapse, after applying cure

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplant; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison.
Notes: placebo refers to the SC arm.

Figure 45. Death from protocol-specified HSCT for adjusted population, censored at relapse, after applying cure

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplant; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison.
Notes: placebo refers to the SC arm.

B.3.3.5 Adverse events

In line with NICE TA523 (105), AEs of grade ≥3 occurring with an incidence of ≥5% were included in the analysis. For quizartinib and SC these were unadjusted for difference in age distribution between trials. AEs were assumed to occur within the first cycle of the model, a simplification which has been used in a previous AML model (101). Incidence rates for AEs for the quizartinib and SC regimens were sourced from the QuANTUM-First trial (21) and the AE rates for midostaurin regimens were sourced from RATIFY (10), as summarised in Table 60.

Table 60. Adverse event frequency (grade ≥3) reported in ≥5% of patients

Adverse event	Quizartinib[a]	SC[a]	Midostaurin[b]
Anaemia	[redacted]	[redacted]	92.7%
Diarrhoea	[redacted]	[redacted]	15.8%
Fatigue	[redacted]	[redacted]	9.0%
Febrile neutropenia	[redacted]	[redacted]	81.7%
Hyperbilirubinemia	[redacted]	[redacted]	7.0%
Hypocalcaemia	[redacted]	[redacted]	6.8%
Hypokalaemia	[redacted]	[redacted]	13.8%
Hyponatraemia	[redacted]	[redacted]	8.7%
Hypophosphataemia	[redacted]	[redacted]	5.4%
Increased alanine aminotransferase	[redacted]	[redacted]	12.7%
Infection	[redacted]	[redacted]	52.4%
Leukopenia	[redacted]	[redacted]	26.2%
Lymphopenia	[redacted]	[redacted]	19.2%
Mucositis or stomatitis	[redacted]	[redacted]	6.2%
Nausea	[redacted]	[redacted]	5.6%
Neutropenia	[redacted]	[redacted]	95.2%
Pain	[redacted]	[redacted]	13.2%
Pneumonitis or pulmonary infiltrates	[redacted]	[redacted]	7.9%
Rash or desquamation	[redacted]	[redacted]	14.1%
Thrombocytopenia	[redacted]	[redacted]	97.5%
Neutrophil count decreased	[redacted]	[redacted]	0.0%
Sepsis	[redacted]	[redacted]	0.0%
Gamma-glutamyl transferase increased	[redacted]	[redacted]	0.0%
Platelet count decreased	[redacted]	[redacted]	0.0%
Hypertension	[redacted]	[redacted]	0.0%
Reference	Daiichi Sankyo 2022		Stone et al. 2017

Abbreviations: SC, standard chemotherapy.
References: Daiichi Sankyo, 2022 (73); Stone et al. 2017 (10)
Notes: a. Data reported in this table includes grade ≥3 treatment-emergent AES that occurred in ≥ 5% of patients in QuANTUM-First trial (Erba et al. 2023); b. Data reported in this table includes grade 3, 4 or 5 AEs that occurred in ≥ 5% of patients in midostaurin's pivotal trial (RATIFY) reported in Stone et al., 2017.

HSCT is associated with a range of complications, the most serious of these is GVHD, a life-threatening AE, which affects approximately 40% of HSCT recipients (105, 123). As a result, the AE of GVHD was explicitly included the model, in line with TA523. This

AE was applied in the first cycle of HSCT (1L and 2L). The GVHD rates were sourced from QuANTUM-First and RATIFY (Table 61).

Table 61. Frequency of GVHD during the HSCT period

Adverse event	Quizartinib[a]	SC[a]	Midostaurin[b]
GVHD	[redacted]	[redacted]	39.0%

Abbreviations: GVHD, graft-versus-host disease; SC, standard chemotherapy.
References: Daiichi Sankyo (73); Wingard et al. 2011 (123); NICE, 2018 (105)
Notes: a. GVHD rate during the HSCT period in subjects who underwent protocol-specified HSCT (safety analysis set) b. The incidence rate was based on Wingard et al. 2011 in line with TA523.

The costs and disutility associated with AEs are described in section B.3.5.6 and section B.3.4.5, respectively.

B.3.3.6 Background mortality

The age-dependent background (or general population) all-cause mortality was applied to all non-death health states in the model. Background mortality was estimated from the most recent UK life tables published by the Office for National Statistics (ONS), 2018-2020 (124) and adjusted by the sex to reflect the model population (Table 45). The background mortality was applied to all non-death health states in the model.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL data was collected in the QuANTUM-First trial as an exploratory endpoint of the trial to assess the impact of quizartinib on PROs (section B.2.6.3). However, As mentioned in section B.2.6.3, the QuANTUM-First study was not designed to formally compare the treatment impact of quizartinib on PRO measures to that of placebo when combined with standard chemotherapy. Given the exploratory nature of the PRO analyses in Q-F , utility values from the literature were applied in the model in line with TA523(105).

B.3.4.2 Health-related quality-of-life studies

An SLR was conducted to assess published literature that characterises the impact of *FLT3*+ AML on HRQoL, the details of which are described in Appendix H. A summary of the utility data identified and used in the model is provided in B.3.4.4.

B.3.4.3 Mapping

Utility values used in the model for HSCT treatment, recovery, and post-HSCT maintenance were mapped from published EORTC QLQ-C30 data (Grulke, et al. 2012 (113)) using an algorithm developed by Crott, et al. (2010) (125), which calculated EQ-5D utility based on QLQ-C30 scores. The QLQ-C30 data published by Grulke, et al. presented scores specific to different stages of stem cell therapy (before HSCT, during hospitalisation, up to 6 months after HSCT and >1 year after HSCT). The algorithm developed by Crott, et al. (presented below) was then applied to these data in order to obtain EQ-5D utility scores:

$$\begin{aligned}&\textit{EQ-5D utility} = 0.85927770 - 0.0069693*(\textit{Physical Functioning}) - \\ &0.0087346*(\textit{Emotional Functioning}) - 0.0039935*(\textit{Social Functioning}) + \\ &0.0000355*(\textit{Physical Functioning})^2 + 0.0000552*(\textit{Emotional Functioning})^2 + \\ &0.0000290*(\textit{Social Functioning})^2 + 0.0011453*(\textit{Constipation}) \\ &+0.0039889*(\textit{Diarrhoea}) + 0.0035614*(\textit{Pain}) - 0.0003678*(\textit{Sleep}) - \\ &0.0000540*(\textit{Diarrhoea})^2 + 0.0000117*(\textit{Sleep})^2\end{aligned}$$

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state-specific utility values were derived from the literature for 1L states in line with TA523 (105) and their sources. As described in the model structure section, to incorporate time-varying post-HSCT survival data from the QuANTUM-First study, the tunnel states of HSCT consequent to first-line therapy - which allowed for differential timing of transplant and modulating peri-event utility - have been removed. The utility value for HSCT 1L state is then derived from the average of three relevant health states (SCT treatment, SCT recovery, and posy-SCT recovery) in TA523. This step was not necessary for 2L HSCT since in the absence of time-varying TPs following 2L treatment tunnel states were utilised. However, due to the lack of dedicated estimates from the literature the 2L HSCT health states were assumed to be valued at 90% of their respective 1L state's utility from TA523, which was validated by a clinical expert (12). The utility values used in the model are summarised in Table 62.

To account for utility deterioration associated with aging, the multiplier method outlined in NICE DSU 12 was applied to the cohort as they progressed through the model (126). The general population utility adjustment was sourced from the Health Survey for England 2014 dataset (122). This method also considers the distribution between male and female patients, thus implicitly weighting for the baseline gender distribution in the modelled population.

Table 62. Summary of utility values for cost-effectiveness analysis

Utility state	Utility values	Reference
Induction	0.648	Uyl-de Groot et al. 1998 (111) in Tremblay et al. 2018 (99) and TA523 (105)
Refractory	0.530	Pan et al. 2010 (110) in Tremblay et al. 2018 (99) and TA523 (105)
Consolidation	0.710	Batty et al. 2014 (112) in Tremblay et al. 2018 (99) and TA523 (105)
Maintenance	0.810	Batty et al. 2014 (112) in Tremblay et al. 2018 (99) and TA523 (105)
First CR	0.830	Leunis et al. 2014 (50) in Tremblay (2018) (99) and TA523 (105)
Relapse1	0.530	Pan et al. 2010 (110) in Tremblay (2018) (99) and TA523 (105)
Second CR	0.747	Assumption: 90% of the utility for the 'First CR'
Relapse2	0.477	Assumption: 90% of the utility for the 'Relapse1'
HSCT 1L	0.750	Source for Algorithm—Crott (2010) (125) Source of QLQC30 data—Grulke (2012) (113) Calculation in Midostaurin STA (6) Average of following utility values from TA523: SCT treatment (0.613), SCT recovery (0.810), and Post-SCT recovery (0.826)
HSCT 2L	0.552	Source for Algorithm—Crott (2010) (125) Source of QLQC30 data—Grulke (2012) (113) Calculation in Midostaurin STA (6) Assumption: 90% of the utility value from SCT treatment health state (0.613) in TA523
HSCT recovery 2L	0.729	Source for Algorithm—Crott (2010) (125) Source of QLQC30 data—Grulke (2012) (113) Calculation in Midostaurin STA (6) Assumption: 90% of the utility value from SCT recovery health state (0.810) in TA523
Post-HSCT 2L maintenance	0.743	Source for Algorithm—Crott (2010) (125) Source of QLQC30 data—Grulke (2012) (113) Calculation in Midostaurin STA (6) Assumption: 90% of the utility value from Post-SCT recovery health state (0.826) in TA523

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; QLQC30, Core Quality of Life questionnaire; Relaspe1, first relapse; Relapse 2,second relapse; STA, single technology appraisal; 1L, first line treatment; 2L, second line treatment.
Note: The utilities used are in line with those from TA523 (105)

B.3.4.5 Adverse events

The disutility was not separately considered for AEs because the health state utility values used in the model are assumed to incorporate the impact of AEs experienced during treatment. This approach is based on the approach used in NICE TA523 for midostaurin (6).

As such, the only disutility incorporated in the model was for GVHD as the main post-HSCT AE, per the ERG recommendations from NICE TA523. The disutility for GVHD, shown in Table 63, has been applied to the proportion of patients experiencing GVHD post-HSCT (1L and 2L) in the patients who entering HSCT 1L state and who entering post HSCT 2L maintenance state.

Table 63. Disutility values for GVHD

Adverse Event	Disutility	Duration (days)
GVHD	0.173	57

Abbreviations: GVHD, graft-vs.-host disease.
References: NICE, 2018 (6), Peric et al. 2016 (127)

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify cost and resource use data associated with patients with *FLT3*+ AML from the published literature. This is described in Appendix I.

In line with NICE requirements, the model only considered direct medical costs. Cost and healthcare resource use inputs comprise drug acquisition and administration costs, treatment specific monitoring costs, HSCT procedure costs, disease management costs, AE costs and terminal care costs.

B.3.5.1 Drug acquisition costs

B.3.5.1.1 First line treatment

The quizartinib regimen, the midostaurin regimen and the SC regimen are administered 1L. These regimens are applied in the induction, CR1, HSCT 1L health states. Although only quizartinib acquisition costs are applied in the HSCT 1L state.

In the induction health state, patients receive induction treatment in line with their assigned treatment regimen. Patients can have up to two cycles of induction treatment.

After induction, patients who achieve CR or CRi enter the CR1 health state. On entering CR1, most patients start consolidation treatment for up to four cycles. Those who complete consolidation treatment will continue to take maintenance treatment in the CR1 health state, which lasts up to 36 cycles for the quizartinib and SC regimens, and 12 cycles for the midostaurin regimen. Patients can relapse during any phase of 'CR1' and so they may not complete the full number of consolidation and maintenance treatment cycles.

Patients are allowed to transition into the 'HSCT 1L' health state once they entered the 'CR1' health state (i.e. patients may transition into the 'HSCT' health state without commencement or before completion of consolidation and maintenance treatment). As described in section B.3.3.2.2, the model assumes that the proportion of patients receiving HSCT is a function of complete response, with all HSCTs completed by cycle 4. Following the HSCT procedure, patients assigned to the quizartinib regimen can

receive quizartinib monotherapy as per trial design. The model further assumes that patients will begin post-HSCT maintenance therapy after 3 cycles. This approach aligns with TA523 and is supported by data from the QuANTUM-First trial, where subjects who underwent HSCT were to begin maintenance therapy anytime between 30 and 180 days after the transplant (equivalent to 1-6.4 28-day cycles). Therefore, it is assumed that post-HSCT maintenance treatment starts from model cycle 7.

Patients assigned to SC regimens do not receive any maintenance treatment post-HSCT in line QuANTUM-First and patients assigned to the midostaurin regimen also do not receive maintenance treatment post-HSCT as midostaurin is not licensed or recommended in this population.

Drug acquisition costs were calculated based on the drug costs per treatment regimen. Where possible these drug costs were extracted from the England based eMIT database (128). Where data could not be identified from eMIT, the British National Formulary (BNF) was used (129). Table 64 describes the pack size and pack costs for each intervention in 1L in the model.

Table 64. Summary of pack size and cost for each intervention in 1L

Treatment	Pack size	Pack cost	Cost per mg	Reference
Quizartinib	17.7 mg x 28	[redacted]	[redacted]	Daiichi Sankyo 2023
	26.5 mg x 56	[redacted]	[redacted]	Daiichi Sankyo 2023
Midostaurin	25 mg x 56	£5,609.94	£4.01	BNF 2023
Cytarabine	500 mg/vial x 5	£16.44	£0.01	eMIT 2023
Daunorubicin	20 mg/vial x 10	£715.00	£3.58	BNF 2023
Idarubicin	10 mg/vial x 1	£138.00	£13.8	eMIT 2023
Sorafenib	200mg x 112	£822.10	£0.11	eMIT 2023

Abbreviations: Admin, administration route; BNF, British National Formulary; eMIT, electronic market information tool; IV, intravenous; 1L, first-line treatment.
References: BNF, 2023 (129), eMIT, 2023 (128), Daiichi Sankyo, 2023 (1)
Notes: the quizartinib price provided is the PAS price

The dosing schedules for the quizartinib regimen, the midostaurin regimen and the SC regimen are described in Table 65.

In the context of anthracycline selection during the induction phase in the model, patients receiving quizartinib and SC were modelled to consider either daunorubicin or idarubicin, with the percentages derived from the QuANTUM-First study (Table 65). In contrast, midostaurin is solely associated with daunorubicin, as indicated by the RATIFY trial. It is assumed that there is no systematic difference in the patient population or in relative clinical efficacy between choosing daunorubicin and Idarubicin. Therefore, the choice of anthracycline treatment will only influence the associated costs.

Relative dose intensity (RDI) refers to the proportion of the intended dose which was administered in practice. For quizartinib and SC RDI was extracted from QuANTUM-First while RDI for midostaurin was taken from the NICE TA523 for midostaurin (Table 65) (6). As previously mentioned, patients in the quizartinib arm of the QuANTUM-First trial could receive quizartinib in the maintenance phase regardless of whether HSCT was received. In the RATIFY trial, only patients who did not undergo HSCT could receive midostaurin in the maintenance phase while patients who underwent HSCT were not allowed to resume midostaurin after HSCT. Consequently, drug acquisition costs are applied to the quizartinib regimen post HSCT (in [redacted] of patients – DS data on file) but not to the midostaurin regimen (98).

Table 65. Dosing schedule, administration route, and RDI for the 1L treatment regimens in the CEM

Treatment		Dosing schedule[a]	Administration	RDI (%)
Quizartinib				
Induction Phase (up to two cycles[b])				
Quizartinib		35.4 mg/day; For 14 days, once daily	Oral	[redacted]
Cytarabine		200 mg/m2/day[c]; Total of 7 days (Day 1 until Day 7)	Continuous IV infusion	[redacted]
Anthracycline regimens: choice of one of the following:	Daunorubicin (46.4%)	60 mg/m^2/day; On Days 1,2 and 3	IV	[redacted]
	Idarubicin (53.6%)	12 mg/m^2/day; On Days 1, 2 and 3	IV	[redacted]
Consolidation phase (four cycles)				
Quizartinib		35.4 mg/day[d]; For 14 days, once daily. Starting on Day 6	Oral	[redacted]
Cytarabine (4 cycles)		Cytarabine 3.0 g/m^2, every 12 hours[d]; On Days 1, 3, and 5 for a total of 6 doses	IV	[redacted]
Maintenance phase (up to 36 cycles)				
Quizartinib (Day 1 -15)		26.5 mg/day; Once daily starting on Day 1	Oral	[redacted]
Quizartinib (Day 16 until cycle 36)		53 mg/day; Once daily starting on Day 16 until cycle 36	Oral	[redacted]
Midostaurin[e]				
Induction				
Midostaurin		50 mg twice a day; On Days 8-21	Oral	95
Cytarabine		200 mg/m^2/day; Total of 7 days (Day 1 until Day 7)	Continuous IV infusion	100
Daunorubicin		60 mg/m^2/day; On Days 1, 2 and 3	IV	100
Consolidation				
Midostaurin		50 mg twice a day; On Days 8-21	Oral	95
High dose cytarabine		3 g/m^2 twice daily; Total of 3 days (Day 1, 3 and Day 5)	Continuous IV infusion	100
Maintenance phase (up to 12 cycles)[d]				
Midostaurin		50 mg/twice a day; On Days 1-28	Oral	95

Treatment		Dosing schedule[a]	Administration	RDI (%)
Sorafenib		Dose level 1 (starting dose): 200 mg twice daily; for 2 weeks Dose level 2 (escalated dose): 200 mg three times daily; for 4 weeks Dose level 3 (targeted dose): 200 mg four times daily continues	Oral	100
SC				
Induction[b]				
Cytarabine		200 mg/m^2/day[c]; Total of 7 days (Day 1 until Day 7)	Continuous IV infusion	[redacted]
Anthracycline regimens: choice of one of the following:	Daunorubicin (35.8%)	60 mg/m^2/day; On Days 1, 2 and 3	IV	[redacted]
	Idarubicin (64.6%)	12 mg/m^2/day; On Days 1, 2 and 3	IV	[redacted]
Consolidation				
Cytarabine (4 cycles, if tolerated)		3.0 g/m2, every 12 hours[d]; On Days 1, 3, and 5 for a total of 6 doses	IV	[redacted]

Abbreviations: CEM, cost-effectiveness model; IV, intravenous; NA, not applicable; RDI, relative dose intensity; SC, standard chemotherapy.
References: Erba et al. 2023 (76); Erba et al. 2023 (21); Daiichi Sankyo, (73); 2022 Stone et al. 2017 (10); NICE, 2018(6); Griffin et al. 2021 (130); Burchert et al. 2020 {Burchert, 2020 #224}
Notes: the dosing schedules were informed by the QuANTUM-First and RATIFY trials. The RDI and % on anthracyclines were sourced from the QuANTUM-First trial (quizartinib and SC regimen) and TA523 (midostaurin regimen). The % using tx post-HSCT was valued via internal analysis for the quizartinib and SC regimens and from Griffin et al 2021 (130) for the midostaurin regimen.a. each cycle is 28 days in duration b. in QuANTUM-First induction cycle 2 there were two options for chemotherapy administered ('7+3' and '5+3') as outlined in section B.2.3. In the model the '7+3' approach (i.e. the same approach as cycle 1) was assumed to have been used in both cycles of induction. c. in QuANTUM-First cytarabine 100 mg/m^2 /day was stated in the protocol but 200 mg/m^2/day allowed if this is the institutional or local standard. In RATIFY 200 mg/m^2/day was specified in the protocol. In the model a dose of 200 mg/m^2/day was used to be conservative. d. QuANTUM-First dosing was as follows: for subjects <60 years old: cytarabine 3.0 g/m^2, every 12 hours; or for subjects ≥ 60 years old: cytarabine 1.5 g/m2, every 12 hours. In the model the dose was assumed to be that of the <60 years group to be conservative. e. only in patients that do not receive HSCT.

For the quizartinib and SC regimens the mean treatment duration from the QuANTUM-First trial was applied in the model (Table 66). Quizartinib was used as post-HSCT maintenance in the trial but in the placebo (SC) arm patients only received placebo in the maintenance phase, this was reflected in the model. The time on treatment inputs were informed from the DS internal analysis using the IPD from QuANTUM-First.

For midostaurin the mean treatment duration is not publicly available, thus for the induction and consolidation phases it was assumed that the average time on treatment was the same as the mean treatment duration for the quizartinib regimen given that midostaurin and quizartinib are both FLT3i treatments. This assumption was validated by a clinical expert (12). Given midostaurin is not licensed post-HSCT this assumption was not applied in the maintenance phase. Instead, the median duration of exposure in maintenance from the midostaurin SmPC was used to inform the time on treatment for the midostaurin regimen in the maintenance phase as this reflects only patients that did not receive HSCT.

Given the lack of mean treatment duration for sorafenib, the median treatment duration of 34.6 weeks (equivalent to 8.65 28-day cycles) was applied in the sorafenib scenario analysis. This input is sourced from a Phase II trial (SORMAIN) which investigated the efficacy of sorafenib as maintenance therapy after HSCT for FLT3+ AML patients (131) .

Table 66. Mean treatment duration for the 1L treatment

	Mean treatment duration (cycles)					
	Quizartinib		SC		Midostaurin	
	Inputs	Reference	Inputs	Reference	Inputs	Reference
Induction	[redacted]	QuANTUM-First unadjusted	[redacted]	QuANTUM-First unadjusted	[redacted]	Assumed same as quizartinib
Consolidation	[redacted]		[redacted]		[redacted]	
Maintenance, patients without HSCT	[redacted]	Daiichi internal analysis T.5.1.3_EXPO_SAS	0.00	SC is not administered post-HSCT	[redacted]	Midostaurin SmPC
Maintenance, patients with HSCTH	[redacted]		0.00		0.00	Midostaurin is not licensed after HSCT

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CSR, clinical study report; SC, standard chemotherapy; SmPC, summary of product characteristics; 1L, first-line treatment.
References: Daiichi Sankyo, 2022 (73); Novartis Pharmaceuticals UK Limited, 2023 (114); NICE, 2018 (105); NHS England, 2023 (132); Daichi Sankyo, 2024 (116)

A pack or vial does not always contain the exact dose required. To account for this the model incorporates the cost of drug wastage. Wastage is calculated for each treatment by rounding the quantity of drug required for each administration to the nearest whole pill or vial and using this quantity to calculate the corresponding drug cost.

B.3.5.1.2 Subsequent treatment

As validated by UK clinical experts, FLAG-Ida and gilteritinib were considered as the subsequent treatments to include for relapsed/refractory patients in this analysis. The subsequent treatment costs were applied to the refractory, relapse1 and post-HSCT relapse health states. Where possible drug acquisition costs were extracted from the England based eMIT database (128). Where data could not be identified from eMIT, the BNF was used (129). A weighted average per cycle subsequent treatment cost was calculated based on the distribution of subsequent treatments (Table 68).

Table 67. Summary of pack size and cost for each intervention in subsequent treatment

Treatment	Pack size	Pack costs	Cost per mg	Reference
FLAG-Ida				
Filgrastim (G-CSF)	0.48 mg/vial x 5	£399.50	£166.46	BNF 2023
Fludarabine	50 mg/vial x 1	£15.88	£0.32	eMIT 2023
Cytarabine	500 mg/vial x 5	£16.44	£0.01	eMIT 2023
Idarubicin	10 mg/vial x 1	£138.00	£13.8	eMIT 2023
Gilteritinib				
Gilteritinib	40 mg x 84	£14,188.00	£4.22	BNF 2023

Abbreviations: Admin, administration route; BNF, British National Formulary; eMIT, electronic market information tool; FLAG-Ida, fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; G-CSF, granulocyte colony stimulating factor; IV, intravenous.
References: BNF, 2023 (129), eMIT, 2023 (128)

The dosing schedules applied in the model and the proportion of patients receiving each regimen is outlined in Table 68. The dosing schedule was assumed to be the same for the refractory, relapse1, and post-HSCT relapse health states and across all model arms. It was assumed that no maintenance treatment was received in post-HSCT treatment in 2L. The distribution of treatments outlined in Table 68 was not equal between arms but depended on the 1L treatment regimen received. This

distribution was from clinical expert advice (12) and was on the basis that a patient would be more likely to receive a 2nd generation FLT3i (i.e. gilteritinib) at 2L if a 2nd generation FLT3i (e.g. quizartinib) wasn't already received at 1L. As a result, patients that receive the midostaurin regimen (midostaurin being a 1st generation FLT3i) would be more likely to receive gilteritinib in 2L than those that receive the quizartinib regimen.

The mean time on subsequent treatment is sourced from the ADMIRAL (Perl et al., 2019) trial which investigated the efficacy of gilteritinib vs. salvage chemotherapy in patients with relapsed or refractory *FLT3*+ AML (118) (Table 68). FLAG-Ida was one of the treatments offered to patients in the salvage chemotherapy arm of the trial. The median treatment duration of treatment of gilteritinib and salvage chemotherapy were used to inform the duration of treatment of gilteritinib and FLAG-Ida applied in the model. The RDI of gilteritinib applied in the model was sourced again from the ADMIRAL trial. However, data for FLAG-Ida was not available and thus the RDI was assumed to be 100%. Wastage is accounted for 2L in the same way as in 1L.

Table 68. Dosing schedule, administration route, treatment distribution, mean time on treatment and RDI for the subsequent treatment regimens in the CEM

	Treatment	Dosing schedule	Administration	2L treatment distribution according to1L treatment choice[a]			Mean time on treatment (cycles)[b]	RDI[b]
				1L quiz	**1L SC**	**1L mido**		
FLAG-Ida	Filgrastim (G-CSF)	300 µg/m^2/day; Total of 5 days (Day 1 until Day 5)	Continuous IV infusion	60%	50%	40%	1.00	100%
	Fludarabine	30 mg/m^2/day; Total of 5 days (Day 2 until Day 6)	IV					100%
	Cytarabine	2000 mg/m^2/day; Total of 5 days (Day 2 until Day 6)	Continuous IV infusion					100%
	Idarubicin	10 mg/m^2/day; Total of 3 days (Day 2 until Day 4)	IV					100%
Gilteritinib	Gilteritinib	120 mg/day; Once daily for 18 weeks (4.5 cycles)	Oral	40%	50%	60%	5.00	98%

Abbreviations: CEM, cost-effectiveness model; FLAG-Ida, fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; G-CSF, granulocyte colony stimulating factor; IV, intravenous; 1L, first-line treatment; quiz, quizartinib; mido, midostaurin; RDI, relative dose intensity; SC, standard chemotherapy.
References: Perl et al. 2019 (118). TA642 (101).
Notes: Each cycle is 28 days in duration. a. treatment distribution is based on clinical expert opinion. b. Mean time on treatment for gilteritinib and FLAG-Ida therapy and RDI for gilteritinib were sourced from the ADMIRAL study. RDI for FLAG-Ida was based on an assumption.

B.3.5.2 Treatment administration costs

Table 69 presents the relevant drug administration costs associated with each treatment. No drug administration cost for oral therapies was assumed, which is in line with TA523 (105). The unit administration cost for SC and intravenous (IV) therapy were sourced from the National schedule of NHS costs 2021/22 (108). SC treatment and IV therapy administration costs were applied according to the number of administrations of the treatment per cycle (e.g. cytarabine is administered intravenously seven times during cycle 1, thus the cost applied for cytarabine administration in cycle 1 was 7*£353.64).

Table 69. Subcutaneous and IV drug administration costs

Description	Unit cost	HRG code	Source
Deliver Simple Parenteral Chemotherapy at First Attendance (**Subcutaneous**)	£ 286.71	SB12Z	National schedule of NHS costs – 2021/22 (108)
Deliver more Complex Parenteral Chemotherapy at First Attendance (**IV**)	£ 353.64	SB13Z	

Abbreviations: HRG, Healthcare Resource Group; IV, intravenous; NHS, National Health Service.

B.3.5.3 Treatment monitoring costs

Treatment monitoring costs are applied per cycle. For 1L treatment, based on TA523 (105), these costs would only be accrued in the induction and CR health states. In contrast, for 2L treatment, these costs would only be accrued during refractory or relapse health states.

Treatment monitoring unit costs were sourced from the National schedule of NHS costs - 2021/22 (108), the National Institute for Health and Care Research interactive costing tool and NICE TA523 (adjusted for inflation) (Table 70) (6).

Table 70. Treatment monitoring unit costs

Monitoring item	Unit cost	Reference
Bone marrow aspirates	£162.87	NHS reference cost: Diagnostic Bone Marrow Extraction (SA33Z) - clinical oncology outpatient procedure
Bone marrow biopsies	£546.82	NHS reference cost: Percutaneous Biopsy of Lesion of Bone, 19 years and over (YH31A). Outpatient clinical oncology services
Peripheral blood smears	£242.00	NIHR iCT: 85060 Blood smear; peripheral, interpretation by physician PATHOLOGY
Blood tests	£13.00	NIHR iCT: 85009 Blood count; differential WBC count, buffy coat PATHOLOGY
DNA and RNA extractions for molecular testing	£1.48	TA523, cost in 2017 inflated to 2022 price level
Extractions for cytogenetic testing	£19.00	NIHR iCT: Cytogenetics Analysis including tissue culture; molecular cytogenetics with karyotyping and banding
Serum blood chemistry	£13.00	NIHR iCT 82465 Cholesterol; total, serum or whole blood PATHOLOGY
Red blood cells transfusion	£245.86	NHS reference cost: Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over (SA44A). Outpatient medical oncology services
Platelets transfusion	£245.86	NHS reference cost: Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over (SA44A)
ECGs monitoring	£301.35	NHS reference cost: Electrocardiogram Monitoring or Stress Testing (EY51Z) - clinical oncology outpatient procedure

Abbreviations: DNA, deoxyribonucleic acid; ECG, electrocardiogram; NHS, National Health Service; NIHR iCT, National Institute for Health and Care Research, interactive costing tool; RNA, ribonucleic acid, WBC, white blood cell.
References: NICE, 2018 (105), NHS, 2022 (108); NIHR, 2023 (107)

The frequencies of treatment monitoring usage by treatment line are shown in Table 71. (1L) and Table 72 (2L). The frequencies of treatment monitoring, sourced from NICE TA523 (6) and NICE TA399 (106), during 1L treatment were assumed to be the same across all treatment arms in line with TA523 with the exception of red blood cell transfusions and platelet transfusions in induction. The frequencies of red blood cell transfusions and platelet transfusions in induction treatment with quizartinib were sourced from the company IPD internal analysis and the frequency of monitoring in patients treated with midostaurin was assumed to be the same (133). The 2L treatment monitoring frequencies were sourced from NICE TA399 (106) and NICE TA523 (105) and were assumed to be the same for both the relapse and refractory health states and across the treatment regimens.

Table 71. First line treatment monitoring frequency, per cycle, by treatment arm

Health state	Quizartinib		SC		Midostaurin	
	Induction	First CR	Induction	First CR	Induction	First CR
Bone marrow aspirates	1.09	0.18	1.09	0.18	1.09	0.18
Bone marrow biopsies	0.46	0	0.46	0	0.46	0
Peripheral blood smears	1.05	0.68	1.05	0.68	1.05	0.68
Blood tests	11.26	2.69	11.26	2.69	11.26	2.69
DNA and RNA extractions for molecular testing	1.08	0.15	1.08	0.15	1.08	0.15
Extractions for cytogenetic testing	0.86	0.16	0.86	0.16	0.86	0.16
Serum blood chemistry	10.23	2.61	10.23	2.61	10.23	2.61
Red blood cells transfusion	[redacted]	0.44	7.5	0.44	[redacted]	0.44
Platelets transfusion	[redacted]	0.32	9.5	0.32	[redacted]	0.32

Abbreviations: CR, complete remission; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; SC, standard chemotherapy.
References: Daiichi Sankyo, 2023 (133);, NICE, 2018 (105)
Notes: a. These estimates were sourced from Daiichi Sankyo IPD analysis; data on file. All other estimates were calculated from the average of azacitidine and conventional chemotherapy arms from TA399 (Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts), which was used to inform the monitoring frequencies for respective health states in TA523 and the values here.

Table 72. Second line treatment monitoring frequency in the relapse/refractory health states, per cycle

Test	Frequency
Bone marrow aspirates	0.16
Bone marrow biopsies	0.02
Peripheral blood smears	0.76
Blood tests	7.78
DNA and RNA extractions for molecular testing	0.15
Extractions for cytogenetic testing	0.14
Serum blood chemistry	7.33
Red blood cells transfusion	4.67
Platelets transfusion	5.78

Abbreviations: DNA, deoxyribonucleic acid; RNA, ribonucleic acid.
References: NICE, 2016 (106)
Notes: The average of azacitidine and conventional chemotherapy arms from TA399 (Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts) was used to inform the monitoring frequencies)

ECG monitoring is required in all patients treated with quizartinib but only in patients concurrently receiving medicinal products that can prolong the QT interval in those treated with midostaurin according to their respective SmPC (1, 114). ECG monitoring costs were therefore considered in the model only for patients who initiate the quizartinib regimen. The frequency of which was sourced from the quizartinib SmPC (1) and can be found in Table 73.

Table 73. ECG monitoring frequency

Model cycle	Frequency	Assumption
Induction, cycle 1	5	One prior to initiation. Once weekly during induction
Induction, cycle 2	4	Once weekly during induction
Consolidation, cycle 1-4	4	Once weekly during consolidation
Maintenance, cycle 1	5	One prior to initiation. Once weekly during the first month
Maintenance, cycle 1+	0	

Abbreviations: ECG, electrocardiogram.
Reference: Daiichi Sankyo Inc, 2023 (1)

B.3.5.4 Allogeneic haematopoietic stem cell transplant

The cost of HSCT was calculated as a weighted average of the cost of the different types of HSCT (in those 19 years or over) listed in the NHS reference costs (elective and non-elective inpatient costs were considered) (108). This cost was applied to all patients who received a transplant on entry to the first HSCT health state.

Table 74. Allogeneic haematopoietic stem cell transplant costs

Parameter	Cost	Reference
HSCT procedure unit cost	£39,257.06	National schedule of NHS costs - 2021/22 (108) Peripheral Blood Stem Cell Transplant, Allogeneic, 19 years and over (SA38A, SA39A, SA40Z

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; NHS, National Health Service.
Notes: a. Subjects were permitted to undergo transplantation after CR or CRi was achieved per protocol; b. Transplantation performed during the first complete remission.

HSCT is associated with a serious AE known as GVHD as described in section B.3.3.5. The associated costs are described in Table 75.

Table 75. GVHD event unit costs

Adverse Event	Cost per episode	HRG code
GVHD (post-HSCT event)	£61,023.63	NICE TA523, inflated to the 2021/22 price level

Abbreviations: GVHD, graft-vs.-host disease; HSCT, haematopoietic stem cell transplantation; HRG, health resource group; NICE, National Institute for Health and Care Excellence; NHS,
References: NICE, 2018 (105)

B.3.5.5 Disease management costs

Disease management costs were included in the model to account for the routine monitoring visits and procedures which occur during AML patient's treatment pathway.

The disease management costs were calculated on a per-cycle basis for each health state, taking into account the frequency of occurrence per cycle. The unit costs of disease management were sourced from the PPSRU 2022 report, NHS 2022 reference costs and NICE TA523 (Table 76).

The frequency of resource use for disease management items, by health state, in minutes per cycle is presented in Table 77. The frequency of disease management were primarily informed by NICE TA399 and TA623 which identified these frequencies

using a HCRU questionnaire for resource use (105, 106). Assumptions were made to account for the additional health states used in the quizartinib model:

- Frequency of disease management resource use in the refractory health state was assumed to be equal to that of the relapsed state.
- Frequency of disease management resource use in the CR2, relapse2, HSCT treatment 2L and HSCT recovery 2L health states were assumed to be equal to the HSCT 1L health state.

Additional costs for HSCT and terminal care were also incorporated in the model, as described in sections B.3.5.4 and B.3.5.7.

Table 76. Disease management unit cost

Item	Unit cost	Reference	Cost per minute
CNS haematologist	£68.00	PSSRU (2022) - Hospital based pharmacist (band 7 - advanced nurse)	£1.13
Consultant	£143.00	PSSRU (2022) - Consultant (medical)	£2.38
Day care nurse	£46.00	PSSRU (2022) - GP practice nurse	£0.77
Day care specialist registrar	£73.00	PSSRU (2022) – Registrar	£1.22
District Nurse	£57.00	PSSRU (2022) - Qualified nurse band 6 (specialist)	£0.95
Doctor	£137.00	PSSRU (2022) - Associate specialist	£2.28
Jnr doctor	£50.00	PSSRU (2022) - Foundation doctor FY2	£0.83
Pharmacist	£66.00	PSSRU (2022) - Hospital based pharmacist (band 7 - specialist)	£1.10
Oncology nurse	£68.00	PSSRU (2022) - Hospital based pharmacist (band 7 - advanced nurse)	£1.13
Inpatient day	£473.91	NHS reference costs 2021/2022 HRG Code SA25M - Acute Myeloid Leukaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff	£0.33
***ITD-FLT3* testing**	£150	TA523	N/A

Abbreviations: CC, complication/comorbidity; CNS, central nervous system; FY2, foundation year 2; GP, general practitioner; HRG, Healthcare Resource Group; *ITD-FLT3*, internal tandem duplication FMS-like tyrosine kinase 3; jnr, junior; N/A, not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.
References: NICE, 2018 (105); PSSRU, 2022 (109); NHS, 2022 (108)

Table 77. Frequency of resource use for treatment monitoring items, by health state, in minutes per cycle

Resource use	Initiation	Induction	Refractory	Consolidation	Maintenance	First CR	Relapse	Second CR	Relapse 2	HSCT treatment 1L	HSCT treatment 2L	HSCT recovery 2L	Post HSCT 2L maintenance
CNS haematologist	0.00	66.00	81.00	33.00	33.00	33.00	81.00	33.00	81.00	0.00	0.00	0.00	0.00
Consultant	0.00	62.00	36.00	17.00	17.00	17.00	36.00	17.00	36.00	0.00	0.00	0.00	0.00
Day care nurse	0.00	116.00	138.00	13.00	13.00	13.00	138.00	13.00	138.00	0.00	0.00	0.00	0.00
Day care specialist registrar	0.00	68.00	54.00	28.00	28.00	28.00	54.00	28.00	54.00	0.00	0.00	0.00	0.00
District Nurse	0.00	42.00	35.00	13.00	13.00	13.00	35.00	13.00	35.00	0.00	0.00	0.00	0.00
Doctor	0.00	38.00	20.00	17.00	17.00	17.00	20.00	17.00	20.00	101.00	101.00	101.00	101.00
Jnr doctor	0.00	139.00	66.00	11.00	11.00	11.00	66.00	11.00	66.00	0.00	0.00	0.00	0.00
Pharmacist	0.00	75.00	24.00	2.00	2.00	2.00	24.00	2.00	24.00	0.00	0.00	0.00	0.00
Oncology nurse	0.00	16.00	3.00	0.00	0.00	0.00	3.00	0.00	3.00	0.00	0.00	0.00	0.00
Inpatient day	0.00	12290.00	5702.00	828.00	828.00	828.00	5702.00	828.00	5702.00	0.00	0.00	0.00	0.00
***ITD- FLT3* testing**	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cost per cycle	£150.00	£4,782.05	£2,389.36	£456.98	£456.98	£456.98	£2,389.36	£456.98	£2,389.36	£230.62	£230.62	£230.62	£230.62
Reference/assumption	NICE, 2016(106) NICE, 2018 (105)	NICE, 2016(106); NICE, 2018 (105)	Assumption: same as relapse health state	NICE, 2016(106); NICE, 2018 (105)	NICE, 2016(106); NICE, 2018 (105)	NICE, 2016(106); NICE, 2018 (105)	NICE, 2016(106); NICE, 2018 (105)	Assumption: same as first CR	Assumption: same as relapse health state	NICE, 2016(106); NICE, 2018 (105)	Assumption: same as HSCT 1L	Assumption: same as HSCT 1L	NICE, 2016(106); NICE, 2018 (105)

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CNS, central nervous system; CR, complete remission, *ITD-FLT3*, internal tandem duplication FMS-like tyrosine kinase 3; HSCT, haematopoietic stem cell transplantation; jnr, junior; NICE, National Institute for Health and Care Excellence; 1L, first line; 2L, second line.

B.3.5.6 Adverse events unit costs

The unit costs associated with AEs were sourced from the National schedule of NHS costs 2021/22 (Table 78) (108). The AE unit costs were multiplied by the percentage of patients who experienced each of the AEs (Table 60) to calculate a weighted average cost by treatment regimen. The AE cost is applied as a one-off cost in the first cycle of the model. This is a simplifying assumption since estimating the exact timing of AEs is not possible for all comparators relevant to the decision problem.

Table 78. Adverse event costs

Adverse Event	Cost per episode	Source
Anaemia	£490.23	NHS reference costs 2021/2022 HRG Code SA04L - Iron Deficiency Anaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Diarrhoea	£516.39	NHS reference costs 2021/2022 HRG Code FD01J - Gastrointestinal Infections without Interventions, with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Fatigue	£473.91	NHS reference costs 2021/2022 HRG Code SA25M - Acute Myeloid Leukaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Febrile neutropenia	£3,579.00	NICE TA523, inflated to the 2021/22 price level; HRG Code PA45Z - Febrile Neutropenia with Malignancy - Non-elective tariff
Hyperbilirubinemia	£816.73	NHS reference costs 2021/2022 HRG Codes GC01E-F - Liver Failure Disorders without Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Hypocalcaemia	£574.69	NHS reference costs 2021/2022 HRG Codes KC05G-N - Fluid or Electrolyte Disorders, with Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Hypokalaemia	£574.69	NHS reference costs 2021/2022 HRG Codes KC05G-N - Fluid or Electrolyte Disorders, with Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Hyponatremia	£574.69	NHS reference costs 2021/2022 HRG Codes KC05G-N - Fluid or Electrolyte Disorders, with Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Hypophosphatemia	£574.69	NHS reference costs 2021/2022 HRG Codes KC05G-N - Fluid or Electrolyte Disorders, with Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Increased alanine aminotransferase	£816.73	NHS reference costs 2021/2022 HRG Codes GC01E-F - Liver Failure Disorders without Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Infection	£889.89	NHS reference costs 2021/2022 HRG Codes HE81A-C - Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts - weighted average of CC scores 0 to 6+ of non-elective inpatients short stay tariff
Leukopenia	£675.75	NHS reference costs 2021/2022 HRG Codes SA09G-L - Other Red Blood Cell Disorders - weighted average of CC scores 0 to 14+ of non-elective inpatients short stay tariff
Lymphopenia	£1,404.47	NHS reference costs 2021/2022 HRG Codes WH54A-B - Procedures on the Lymphatic System - weighted average of CC scores 0 and 1+ non-elective inpatients short stay tariff
Mucositis or stomatitis	£473.91	NHS reference costs 2021/2022 HRG Code SA25M - Acute Myeloid Leukaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff

Adverse Event	Cost per episode	Source
Nausea	£473.91	NHS reference costs 2021/2022 HRG Code SA25M - Acute Myeloid Leukaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Neutropenia	£473.91	NHS reference costs 2021/2022 HRG Code SA25M - Acute Myeloid Leukaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Pain	£473.91	NHS reference costs 2021/2022 HRG Code SA25M - Acute Myeloid Leukaemia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Pneumonitis or pulmonary infiltrates	£655.45	NHS reference costs 2021/2022 HRG Codes DZ11R-V - Lobar, Atypical or Viral Pneumonia, without Interventions - weighted average of CC scores 0 to 14+ of non-elective inpatients short stay tariff
Rash or desquamation	£602.15	NHS reference costs 2021/2022 HRG Code JC43C - Minor Skin Procedures, 19 years and over - weighted average of non-elective inpatients short stay tariff
Thrombocytopenia	£683.02	NHS reference costs 2021/2022 HRG Code SA12K - Thrombocytopenia with CC Score 0-1 - weighted average of non-elective inpatients short stay tariff
Neutrophil count decreased	£675.75	NHS reference costs 2021/2022 HRG Codes SA09G-L - Other Red Blood Cell Disorders - weighted average of CC scores 0 to 14+ of non-elective inpatients short stay tariff
Sepsis	£731.46	NHS reference costs 2021/2022 HRG Codes WJ06A-J - Sepsis with Multiple Interventions - weighted average of CC scores 0 to 9+ of non-elective inpatients short stay tariff
Gamma-glutamyl transferase increased	£816.73	NHS reference costs 2021/2022 HRG Codes GC01E-F - Liver Failure Disorders without Interventions - weighted average of CC scores 0 to 5+ of non-elective inpatients short stay tariff
Platelet count decreased	£675.75	NHS reference costs 2021/2022 HRG Codes SA09G-L - Other Red Blood Cell Disorders - weighted average of CC scores 0 to 14+ of non-elective inpatients short stay tariff
Hypertension	£424.60	NHS reference costs 2021/2022 HRG Code EB04Z - Hypertension - weighted average of non-elective inpatients short stay tariff

Abbreviations: HRG, healthcare resource group; CC, complication/comorbidity; NHS, National Health Service.
References: NHS, 2022 (108)

B.3.5.7 Terminal care costs

To reflect the additional costs incurred by patients prior to their death, a terminal care cost was also applied to all patients that die in the model. The cost for terminal care was sourced from the PSSRU Unit Costs of Health and Social Care 2022 manual which estimated that the average cost of terminal care from death from any cause was £12,397 (109). This cost was applied as a one-off cost at the time of death irrespective of cause.

B.3.6 Severity

In order to calculate the absolute quality-adjusted life year (QALY) shortfall the total QALYs that people living with a condition would be expected to have with current treatment were subtracted from the expected total QALYs for the general population based on NICE's health technology evaluation guidance development manual (81). The proportional QALY shortfall was calculated by dividing the absolute QALY shortfall into the expected total QALYS for the general population. For the calculation of expected total QALYs for the general population, the survival was based on the 2018-20 National life tables for England and Wales from the ONS (124), while the population EQ-5D-3L data by age and sex were derived from the HSE 2014 dataset, as recommended in the NICE DSU report from Hernández Alava et al. (2022) (134). QALYs were discounted using the base-case annual discount rate of 3.5% for health outcomes.

The features of the population used in the QALY shortfall analysis are summarised in Table 79. A summary of health state benefits and utility values used for the QALY shortfall analysis is provided in Table 80. The discounted values of absolute and proportional QALY shortfalls were calculated at 5.1 and 0.4, respectively. Based on the absolute and proportional shortfalls being less than 12 and 0.85 respectively the QALY weighting for severity assigned was '1' (Table 81). No QALY shortfall was reported in TA523 so a comparison vs. previous submissions was not completed.

Table 79. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	[redacted] female	B.3.3.1
Starting age	[redacted]	B.3.3.1

Reference: QuANTUM-First population (individuals under 60 years). Erba et al. 2023 (21); Daiichi Sankyo, 2023 (85).

Table 80. Summary of health state benefits and utility values for QALY shortfall analysis

Health state	Utility inputs	Undiscounted life years	
		Standard chemotherapy (Placebo)	Midostaurin
Induction	0.648	[redacted]	[redacted]
Refractory	0.530	[redacted]	[redacted]
First CR	Consolidation: 0.710 Maintenance: 0.81 First CR: 0.830	[redacted]	[redacted]
Relapse 1	0.530	[redacted]	[redacted]
Second CR	0.747	[redacted]	[redacted]
Relapse 2	0.477	[redacted]	[redacted]
HSCT 1L	0.750	[redacted]	[redacted]
Relapse after HSCT 1L	0.477	[redacted]	[redacted]
HSCT 2L	0.552	[redacted]	[redacted]
HSCT recovery 2L	0.729	[redacted]	[redacted]
Post-HSCT 2L maintenance	0.743	[redacted]	[redacted]
Total	N/A	[redacted]	[redacted]

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; N/A, not applicable; QALY, quality adjusted life year; 1L, first-line treatment; 2L, second-line treatment.
Notes: The utility inputs and their sources can be found in Table 62.

Table 81. Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Midostaurin	[redacted]	[redacted]	7.4	0.6
SC	[redacted]	[redacted]	8.5	0.7

Abbreviations: QALY, quality adjusted life year; SC, standard chemotherapy.
References: Office for National Statistics 2023 (124); University of Sheffield, 2022 (122)

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

Table 82. Summary of variables applied in the economic model

Variable	Value		Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Model parameters					
Discount rate for costs and effects	3.5%		N/A	None	B.3.2.2
Baseline characteristics of patient population					
Female	[redacted]		[redacted]	Beta	B.3.3.1
Male	[redacted]		[redacted]	N/A	
Age at start	47.0 years		0.74 years	Lognormal	
Mean bodyweight	[redacted]		[redacted]	Lognormal	
Mean height	[redacted]		[redacted]	Lognormal	
Mean body surface area	[redacted]		[redacted]	None	
Transition probabilities – quizartinib, %					
First induction round to:	Induction	Residual	N/A	None	B.3.3.2.1
	First CR	[redacted]	[redacted]	Beta	
	Refractory	[redacted]	[redacted]		
	Death	[redacted]	[redacted]		
Second induction round to:	Induction	0.0	0.000	None	
	First CR	[redacted]	[redacted]	Beta	
	Refractory	Residual	N/A	None	
	Death	[redacted]	[redacted]	Beta	
CR1 to:	CR1	Residual	N/A	None	B.3.3.2.2
	Relapse1	Based on relapse from CRc curve	N/A	None	
	HSCT 1L	[redacted]	[redacted]	Beta	
	Death (time-varying)	Based on death from CRc curve	N/A	None	
HSCT 1L to:	Post-HSCT relapse1	[redacted]	[redacted]	Beta	B.3.3.2.3
	Death (time-varying)	Based on death from CRc curve	N/A	None	
2L post-HSCT maintenance to:	Post-HSCT relapse2	[redacted]	[redacted]	Beta	
	Death	[redacted]	[redacted]	Beta	
Refractory to:	Refractory	Residual	N/A	None	B.3.3.2.4
	CR2	14.3%	0.03	Beta	
	Death	5.2%	0.01		
Relapse1 to:	Relapse1	Residual	N/A	None	
	CR2	30.0%	0.06	Beta	
	Death	[redacted]	[redacted]		
CR2 to:	CR2	Residual	N/A	None	
	Relapse2	2.2%	0.00	Beta	
	HSCT 2L	12.5%	0.03		

Variable	Value		Standard error	Measurement of uncertainty and distribution	Reference to section in submission
	Death	2.8%	0.01		
Relapse2 to:	Relapse2	Residual	N/A	None	
	Death	[redacted]	[redacted]	Beta	
Transition probabilities – SC, %					
First induction round to:	Induction	Residual	N/A	None	B.3.3.2.1
	First CR	[redacted]	[redacted]	Beta	
	Refractory	[redacted]	[redacted]		
	Death	[redacted]	[redacted]		
Second induction round to:	Induction	0.0	N/A	None	
	First CR	[redacted]	[redacted]	Beta	
	Refractory	Residual	N/A	None	
	Death	[redacted]	[redacted]	Beta	
CR1 to:	CR1	Residual	N/A	None	B.3.3.2.2
	R1	Based on the HR applied to the quizartinib relapse from CR curve	N/A	None	
	HSCT 1L	[redacted]	[redacted]	Beta	
	Death (time-varying)	Based on the HR applied to the quizartinib death from CRc curve	N/A	None	
HSCT 1L to:	Post-HSCT relapse1	[redacted]	[redacted]	Beta	B.3.3.2.3
	Death (time-varying)	Based on death from CRc curve	N/A	None	
2L post-HSCT maintenance to:	Post-HSCT relapse2	[redacted]	[redacted]	Beta	
	Death	[redacted]	[redacted]	Beta	
Refractory to	Refractory	Residual	N/A	None	B.3.3.2.4
	CR2	14.3%	0.03	Beta	
	Death	30.8%	0.00		
Relapse1 to:	Relapse1	Residual	N/A	None	
	CR2	[redacted]	[redacted]	Beta	
	Death	5.2%	0.01		
CR2 to:	CR2	Residual	N/A	None	
	Relapse2	2.2%	0.00	Beta	
	HSCT 2L	12.5%	0.03		
	Death	2.8%	0.01		
Relapse2 to:	Relapse2	Residual	N/A	None	
	Death	5.2%	0.01	Beta	
Transition probabilities – midostaurin, %					
First induction round to:	Induction	Residual	N/A	None	B.3.3.2.1
	First CR	[redacted]		Lognormal	
	Refractory	[redacted]		None	
	Death	[redacted]			
Second induction round to:	Induction	0.0	0.00	None	
	First CR	[redacted]	N/A	Lognormal	
	Refractory	Residual		None	

Variable	Value		Standard error	Measurement of uncertainty and distribution	Reference to section in submission
	Death	[redacted]			
CR1 to:	CR1	Residual	N/A	None	B.3.3.2.2
	R1	Based on HR applied to relapse from CRc curve			
	HSCT 1L	34.1%	0.04	Beta	
	Death (time-varying)	HR (time-varying)	N/A	None	
HSCT 1L to:	Post-HSCT relapse1	[redacted]	[redacted]	Beta	B.3.3.2.3
	Death (time-varying)	Based on death from CRc curve	N/A	None	
2L post-HSCT maintenance to:	Post-HSCT relapse2	[redacted]	[redacted]	Beta	
	Death	[redacted]	[redacted]	Beta	
Refractory to:	Refractory	Residual	N/A	None	B.3.3.2.4
	CR2	14.3%			
	Death	5.2%			
Relapse1 to:	Relapse1	Residual			
	CR2	30.0%			
	Death	[redacted]			
CR2 to:	CR2	Residual			
	Relapse2	2.2%			
	HSCT 2L	12.5%			
	Death	2.8%			
Relapse2 to:	Relapse2	Residual			
	Death	5.2%			
HSCT transition probability (%) of disease related death (per cycle)					
HSCT, tunnel state 1	3.7%		0.01	Beta	B.3.3.2
HSCT, tunnel states 2-3	4.2%		0.01		
HSCT recovery, tunnel states 1-10	2.4%		0.00		
Post-HSCT recovery	0.4%		0.00		
Comparator efficacy inputs					
CIR HR for relapse from CRc: quizartinib vs. midostaurin	[redacted] 95% CI: [redacted]		[redacted]	Lognormal	B.3.3.3.1
CIR HR for relapse from CRc: quizartinib vs. SC	[redacted] 95% CI: [redacted]		[redacted]		
OS HR for death from CRc: quizartinib vs. midostaurin	[redacted] 95% CI: [redacted]		[redacted]		B.3.3.3.2
OS HR for death from CRc: quizartinib vs. SC	[redacted] 95% CI: [redacted]		[redacted]		
Adverse event rates – quizartinib, %					
Anaemia	[redacted]		[redacted]	Beta	B.3.3.5
Diarrhoea	[redacted]		[redacted]		
Fatigue	[redacted]		[redacted]		
Febrile neutropenia	[redacted]		[redacted]		

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Hyperbilirubinemia	[redacted]	[redacted]		
Hypocalcaemia	[redacted]	[redacted]		
Hypokalaemia	[redacted]	[redacted]		
Hyponatraemia	[redacted]	[redacted]		
Hypophosphataemia	[redacted]	[redacted]		
Increased alanine aminotransferase	[redacted]	[redacted]		
Infection	[redacted]	[redacted]		
Leukopenia	[redacted]	[redacted]		
Lymphopenia	[redacted]	[redacted]		
Mucositis or stomatitis	[redacted]	[redacted]		
Nausea	[redacted]	[redacted]		
Neutropenia	[redacted]	[redacted]		
Pain	[redacted]	[redacted]		
Pneumonitis or pulmonary infiltrates	[redacted]	[redacted]		
Rash or desquamation	[redacted]	[redacted]		
Thrombocytopenia	[redacted]	[redacted]		
Neutrophil count decreased	[redacted]	[redacted]		
Sepsis	[redacted]	[redacted]		
Gamma-glutamyl transferase increased	[redacted]	[redacted]		
Platelet count decreased	[redacted]	[redacted]		
Hypertension	[redacted]	[redacted]		
GVHD after HSCT	[redacted]	[redacted]		
Adverse event rates – SC, %				
Anaemia	[redacted]	[redacted]	Beta	B.3.3.5
Diarrhoea	[redacted]	[redacted]		
Fatigue	[redacted]	[redacted]		
Febrile neutropenia	[redacted]	[redacted]		
Hyperbilirubinemia	[redacted]	[redacted]		
Hypocalcaemia	[redacted]	[redacted]		
Hypokalaemia	[redacted]	[redacted]		
Hyponatraemia	[redacted]	[redacted]		
Hypophosphataemia	[redacted]	[redacted]		
Increased alanine aminotransferase	[redacted]	[redacted]		
Infection	[redacted]	[redacted]		
Leukopenia	[redacted]	[redacted]		
Lymphopenia	[redacted]	[redacted]		
Mucositis or stomatitis	[redacted]	[redacted]		
Nausea	[redacted]	[redacted]		
Neutropenia	[redacted]	[redacted]		
Pain	[redacted]	[redacted]		
Pneumonitis or pulmonary infiltrates	[redacted]	[redacted]		
Rash or desquamation	[redacted]	[redacted]		
Thrombocytopenia	[redacted]	[redacted]		

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Neutrophil count decreased	[redacted]	[redacted]		
Sepsis	[redacted]	[redacted]		
Gamma-glutamyl transferase increased	[redacted]	[redacted]		
Platelet count decreased	[redacted]	[redacted]		
Hypertension	[redacted]	[redacted]		
GVHD after HSCT	[redacted]	[redacted]		
Adverse event rates – midostaurin, %				
Anaemia	92.7%	0.19	Beta	B.3.3.5
Diarrhoea	15.8%	0.03		
Fatigue	9.0%	0.02		
Febrile neutropenia	81.7%	0.16		
Hyperbilirubinemia	7.0%	0.01		
Hypocalcaemia	6.8%	0.01		
Hypokalaemia	13.8%	0.03		
Hyponatraemia	8.7%	0.02		
Hypophosphataemia	5.4%	0.01		
Increased alanine aminotransferase	12.7%	0.03		
Infection	52.4%	0.10		
Leukopenia	26.2%	0.05		
Lymphopenia	19.2%	0.04		
Mucositis or stomatitis	6.2%	0.01		
Nausea	5.6%	0.01		
Neutropenia	95.2%	0.19		
Pain	13.2%	0.03		
Pneumonitis or pulmonary infiltrates	7.9%	0.02		
Rash or desquamation	14.1%	0.03		
Thrombocytopenia	97.5%	0.19		
Neutrophil count decreased	0%	0.08		
Sepsis	0%	0.00		
Gamma-glutamyl transferase increased	0%	0.00		
Platelet count decreased	0%	0.00		
Hypertension	0%	0.00		
GVHD after HSCT	39%	0.08		
Utilities				
Induction	0.648	0.13	Beta	B.3.4.4
Refractory	0.530	0.11		
Consolidation	0.710	0.14		
Maintenance	0.810	0.16		
First CR	0.830	0.17		
Relapse	0.530	0.11		
Second CR	0.747	0.15		
Relapse 2	0.477	0.10		
HSCT 1L	0.750	0.12		

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
HSCT 2L	0.552	0.11		
HSCT recovery 2L	0.729	0.15		
Post-HSCT 2L maintenance	0.743	0.15		
Disutilities				
Disutilities for GVHD	0.173	0.03	Beta	B.3.4.5
Drug acquisition costs (per package)				
Quizartinib 17.7 mg, 28 tablets/package	[redacted]	N/A	N/A	B.3.5.1
Quizartinib 26.5 mg, 56 tablets/package	[redacted]	N/A		
Midostaurin 25 mg, 56 tablets/package	£5,609.94	N/A		
Cytarabine 500 mg/vial, 5 vials/package	£16.44	N/A		
Daunorubicin 20 mg/vial, 10 vials/package	£715.00	N/A		
Fludarabine 50 mg/vial, 1 vial/package	£15.88	N/A		
Idarubicin 10 mg/vial, 1 vial/package	£138.00	N/A		
Filgrastim (G-CSF) 0.48 mg/vial, 5 vial/package	£399.50	N/A		
Gilteritinib 40 mg, 84 tablets/package	£14,188.00	N/A		
Mean treatment duration – quizartinib, cycles				
Induction	[redacted]	[redacted]	Gamma	B.3.5.1.1
Consolidation	[redacted]	[redacted]		
Maintenance, patients without HSCT	[redacted]	[redacted]		
Maintenance, post HSCT	[redacted]	[redacted]		
Mean treatment duration – SC, cycles				
Induction	[redacted]	[redacted]	Gamma	B.3.5.1.1
Consolidation	[redacted]	[redacted]		
Maintenance, patients without HSCT	0.00	N/A	None	
Maintenance, post HSCT	0.00	N/A		
Mean treatment duration – midostaurin, cycles				
Induction	[redacted]	[redacted]	Gamma	B.3.5.1.1
Consolidation	[redacted]	[redacted]		
Maintenance, patients without HSCT	11.96	2.39		
Maintenance, post HSCT	0.00	N/A	None	
Treatment monitoring costs (per unit)				
Bone marrow aspirates	£162.87	£32.57	Gamma	B.3.5.3
Bone marrow biopsies	£546.82	£109.36		
Peripheral blood smears	£220.00	£44.00		

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Blood tests	£18.00	£3.60		
DNA and RNA extractions for molecular testing	£1.48	£0.30		
Extractions for cytogenetic testing	£12.00	£2.40		
Serum blood chemistry	£12.00	£2.40		
Red blood cells transfusion	£245.86	£49.17		
Platelets transfusion	£245.86	£49.17		
ECGs monitoring	£301.35	£60.27		
Disease management costs (per unit)				
CNS haematologist	£68.00	£13.60	Gamma	B.3.5.5
Consultant	£143.00	£28.60		
Day care nurse	£46.00	£9.20		
Day care specialist registrar	£73.00	£14.60		
District Nurse	£57.00	£11.40		
Doctor	£137.00	£27.40		
Jnr doctor	£50.00	£10.00		
Pharmacist	£66.00	£13.20		
Oncology nurse	£68.00	£13.60		
Inpatient day	£473.91	£94.78		
ITD-FLT3 testing	£150.00	£30.00		
Adverse event costs (per episode)				
Anaemia	£490.23	£98.05	Gamma	B.3.5.6
Diarrhoea	£516.39	£103.28		
Fatigue	£473.91	£94.78		
Febrile neutropenia	£3,579.00	£808.42		
Hyperbilirubinemia	£816.73	£163.35		
Hypocalcaemia	£574.69	£114.94		
Hypokalaemia	£574.69	£114.94		
Hyponatremia	£574.69	£114.94		
Hypophosphatemia	£574.69	£114.94		
Increased alanine aminotransferase	£816.73	£163.35		
Infection	£889.89	£177.98		
Leukopenia	£675.75	£135.15		
Lymphopenia	£1,404.47	£280.89		
Mucositis or stomatitis	£473.91	£94.78		
Nausea	£473.91	£94.78		
Neutropenia	£473.91	£94.78		
Pain	£473.91	£94.78		
Pneumonitis or pulmonary infiltrates	£655.45	£131.09		
Rash or desquamation	£602.15	£120.43		
Thrombocytopenia	£683.02	£136.60		
Neutrophil count decreased	£675.75	£135.15		
Sepsis	£731.46	£146.29		

Variable	Value	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Gamma-glutamyl transferase increased	£816.73	£163.35		
Platelet count decreased	£675.75	£135.15		
Hypertension	£424.60	£84.92		
GVHD (post-HSCT event)	£61,023.63	£12,204.73		
Other resource costs				
HSCT procedure cost (per unit)	£39,257.06	£7,851.41	Gamma	B.3.5.4
Terminal care cost	£12,397	£2,479.40		B.3.5.7

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CI, confidence interval; CNS, central nervous system; CR, complete remission; CR1, first CR; CR2, second CR; DNA, deoxyribonucleic acid; ECG, electrocardiogram; G-CSF, granulocyte colony stimulating factor; GVHD, graft-vs.-host disease; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; *ITD-FLT3*, internal tandem duplication FMS-like tyrosine kinase 3; jnr, junior; NA, not applicable; OS, overall survival; RFS, relapse-free survival; RNA, ribonucleic acid; Relapse1, first relapse; Relapse2, second relapse SC, standard chemotherapy; 1L, first line; 2L, second line.

B.3.7.2 Assumptions

Table 83 describes the key assumptions applied in the model.

Table 83. Model assumptions

Model characteristics	Base case assumption	Rationale
Population	The QuANTUM-First patient population is reweighted by matching on TEMs in the MAIC analysis (becoming RATIFY-like and termed the adjusted QuANTUM-First population)	MAIC is a population adjusted technique and was used to mitigate the impact of between study heterogeneity. MAIC adjusts for cross-study differences in clinically relevant TEMs and recalculates the efficacy of the treatment (quizartinib), assuming the drug is used in patient populations similar to those of the respective comparator trial (RATIFY). In order to facilitate a meaningful comparison of survival outcomes between quizartinib and midostaurin, this assumption ensured that the adjusted QuANTUM-First population was in alignment with the RATIFY population. Consequently, this also brought it into alignment with the population considered in the MAIC
Treatment regimens	Induction treatment with cytarabine: in QuANTUM-First cytarabine 100 mg/m^2 /day was stated in the protocol but 200 mg/m^2/day was allowed if this was the institutional or local standard. In RATIFY 200 mg/m^2/day was specified in the protocol. In the model a dose of 200 mg/m^2/day was assumed in all regimens (10, 21).	The same dose of standard chemotherapy was applied across all arms. This was considered a conservative approach (as it incurs the highest cost).
	Consolidation treatment with cytarabine: In QuANTUM-First the dose for subjects <60 years old is 3.0 g/m^2, every 12 hours whilst for subjects ≥ 60 years old the dose is 1.5 g/m^2, every 12 hours (both for 3 days). In RATIFY 6 g/m^2/day was specified in the protocol. In the model the dose for the younger population was applied to all patients (i.e. 6 g/m^2/day for 3 days) (10, 21).	This assumption was made to simplify the calculation, which could be considered a conservative approach (as it incurs the highest cost).
	It was assumed that the treatment duration of midostaurin was the same as that of quizartinib (in	In the absence of data on the mean treatment duration of midostaurin an assumption that its mean treatment

Model characteristics	Base case assumption	Rationale
	QuANTUM-First) for the induction and consolidation phases and is per the medium treatment exposure indicated in the midostaurin SmPC in the maintenance phase.	duration would be the same as that of another FLT3i in the induction and consolidation phases seemed reasonable. However, given the differences in use of the two treatments in maintenance post-HSCT using the treatment exposure indicated in the SmPC seemed more reasonable for this phase. The median was assumed to be same as the mean treatment duration. This assumption was validated by a clinical expert (12).
HSCT	The RATIFY trial did not mandate or specify conditions around HSCT (10), so it was assumed that the HSCT rate during the first CR (in CR1) from RATIFY corresponded to the protocol-specified HSCT rate in patients that achieved CRc in QuANTUM-First.	This assumption was made for consistency because analyses for quizartinib and SC use the protocol-specified HSCT data.
	Tunnel states were incorporated within the HSCT 2L state, specifically during HSCT treatment (3 cycles) and HSCT recovery (10 cycles). It was assumed that patients could only transition to the Dead health state during the tunnel states (i.e. relapse was not enabled).	Tunnel states were incorporated to account for variations in costs and utilities within this health state, in alignment with the methodology applied in TA523. It was assumed that the rate of relapse would be zero during these tunnel states.
	It was assumed that patients who received HSCT in 1L treatment could not receive HSCT in 2L in the model.	This was in line with clinical expert opinion which advised that a negligible proportion of patients would receive a second treatment with HSCT (12).
Second-line treatment	The distribution of salvage treatments in R/R by treatment regimen as outlined in Table 68.	This was based on clinical expert opinion on the basis that a patient would be more likely to receive a 2nd generation FLT3i (i.e., gilteritinib) at second line if a 2nd generation FLT3i (e.g., quizartinib) wasn't already received in first line. As a result, patients that receive the midostaurin regimen (midostaurin being a 1st generation FLT3i) would be more likely to receive gilteritinib in second line than those that receive the quizartinib regimen (12).
	The dosing schedule of each 2L treatment (with FLAG-Ida or gilteritinib as outlined in section	The ELN 2022 (43) treatment guidelines (recognised as the main guidelines followed for the management of

Model characteristics	Base case assumption	Rationale
	B.3.5.1.2) was assumed to be the same for the refractory and remission health states.	AML in the UK) indicate that patients that are refractory or relapse would receive the same treatment regimens.
	It was assumed that no maintenance treatment was received in post-HSCT treatment in 2L.	According to NICE TA642 gilteritinib should not be given as maintenance therapy after an HSCT (104).
Transition probabilities	Where ITC results were not available TPs in 1L for midostaurin were assumed to be the same as those of the quizartinib regimen (other than for 1L and 2L post-HSCT).	Where comparative efficacy data is unavailable for midostaurin equivalence with quizartinib is a conservative assumption given clinical expert opinion suggests that quizartinib would have an improved efficacy as compared to midostaurin since quizartinib is a 2nd generation FLT3-ITD targeted treatment. Post-HSCT it is assumed that midostaurin would have the same relapse rate as SC given that maintenance treatment is not given post-HSCT in the midostaurin regimen.
	It was assumed that the CR events, which occurred after exceeding 56 days (i.e., two induction cycles) in the QuANTUM-First, happened in the second round of induction in the model.	This simplifies model calculations and patient flow. Patients achieving CR after 56 days account for only a sixth of the total number of patients in the second round of induction, thus the impact is expected to be limited
	Transitions from 2L states to death were assumed to be time invariant.	IPD data were not available from ADMIRAL (118).
	Transitions from Relapse2 to death were assumed to be the same as those from Relapse1 to death.	Lack of data from literature. Assumption validated by clinical expert.
Cure modelling	Patients in long term remission (≥3 years) are assumed to be cured.	NICE TA523 and TA642 applied similar methods to model cure. TA523 and TA642 applied a cured state after 3 years (later adjusted to 2 years in TA642) and suggested because AML is an aggressive disease most relapse and death occur early in treatment (103, 104). The committee indicated in TA523 that it would prefer to use the ‘latest point at which the data showed a levelling out effect because this was more logically a point of 'cure'' (6). In QuANTUM-First a levelling-out effect was

Model characteristics	Base case assumption	Rationale
		observed in the OS data at three years (21).The committee indicated in TA523 that it would prefer to use the 'latest point at which the data showed a levelling out effect because this was more logically a point of 'cure'' (6). In QuANTUM-First a levelling-out effect was observed in the OS data at three years (21). Clinical validation has further indicated that three years was an acceptable cure point (12).
	A twofold increase in mortality as compared with the general population mortality was applied to 'cured' patients in the quizartinib model.	This is in line with TA523 in which the committee agreed that the mortality rate for people whose disease had been 'cured' would likely be higher than that of the general population mortality rate (7). As a result, a twofold increase in mortality as compared with the general population mortality was applied to 'cured' patients in TA523. This rate was also applied in TA642.
	After the cure point it was assumed that no further costs would be accrued and that utilities would be in line with those of the general population.	This approach is in line with previous submissions (TA523 and TA642) • In TA523 the committee agreed that their preferred approach was that no health state costs were applied after the cure point • Similarly, in TA642 (other than a once-only cost of treating disease progression) the model assumed that all disease management costs were zero after the assumed 3-year cure point • In TA642 it was assumed that patients would be of perfect health (prior to age adjustment) post cure point.
Costs	Oral tablets were assumed to be associated with no administration costs.	They are self-administered. This is in line with the approach taken in TA523 (105).
AEs	AEs of grade ≥3 occurring with an incidence of ≥5% were included in the analysis.	This is in line with the approach followed in TA523 (105).
	Disutilities associated with AEs are not applied in the	This is in line with the approach followed in TA523 (105).

Model characteristics	Base case assumption	Rationale
	model.	The TA523 model used utility values specific to each phase (induction, consolidation, CR, etc.) and these were assumed to include the disutilities for toxicities during treatment.
Utility values	2L utilities are assumed to be 90% of the 1L values.	Literature was not identified for 2L utilities. This assumption was validated by a clinical expert (12).
Disease management	Assumptions were made to account for the additional health states used in the quizartinib model as compared to the TA523 model: • Frequency of resource use in the refractory health state was assumed to be equal to that of the relapsed state • Frequency of resource use in the CR2, Relapse2, HSCT treatment 2L and HSCT recovery 2L health states were assumed to be equal to their equivalent 1L health states.	The ELN guidelines (8) indicate that the recommended treatments are aligned between relapsed and refractory patients thus treatment monitoring is expected to be similar between these patients Evidence was not available for the frequency of resource use in 2L. This is a conservative assumption.

Abbreviations: AE, adverse event; HSCT, allogeneic haematopoietic stem cell transplant; AML, acute myeloid leukaemia; CR, complete remission; CR1, first CR; CR2, second CR; EAG, external assessment group; ELN, European LeukemiaNet; ERG, evidence review group; FLAG-Ida, Fludarabine, Cytarabine, Idarubicin and granulocyte-colony stimulating factor; GVHD, graft-vs.-host disease; HCRU, healthcare resource utilisation; IPD, individual patient data; ITC, indirect treatment comparison; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; NIHR iCT, National Institute for Health and Care Research, interactive costing tool; PSSRU, Personal Social Services Research Unit; PartSA, partitioned survival analysis; Relapse 1, first relapse; Relapse2, second relapse; STA, single technology appraisal; SC, standard chemotherapy; UK, United Kingdom; 1L, first line; 2L, second line.
References: NICE, 2018 (105)

B.3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

All results presented include the proposed quizartinib patient access scheme (PAS) price. NHS List prices are used for the comparators.

The deterministic base case results applying the quizartinib PAS price are presented in Table 84. The quizartinib regimen resulted in a gain of [redacted] and [redacted] LYs when compared to the midostaurin and SC regimens respectively. A gain in QALYs was also observed in those that received the quizartinib regimen (QALY gain vs midostaurin: [redacted]; QALY gain vs SC: [redacted]). These additional LYs and QALYs with the quizartinib regimen are achieved with cost savings of [redacted] compared to the midostaurin regimen and additional costs compared to the SC regimens of [redacted]. The model results show that quizartinib is dominant compared to midostaurin. The results show that quizartinib is more effective and more costly than SC with an ICER £15,851/QALY gained.

The fully incremental analyses confirm that quizartinib is a cost-effective alternative to midostaurin and SC (Table 85). Use of the quizartinib regimen resulted in an additional [redacted] QALYs and [redacted] LYs compared with SC and the use of the midostaurin regimen resulted in [redacted] QALYs less and [redacted] LYs less than with the quizartinib regimen. The additional QALYs for quizartinib over SC were associated with an incremental cost of [redacted] whilst the loss in QALYs with the midostaurin regimen over the quizartinib regimen still resulted in a [redacted] incremental cost.

An assessment of net health benefit of the quizartinib regimen as compared to the midostaurin and SC regimens was also completed. The results suggest that at a willingness-to-pay (WTP) threshold of £30,000/QALY gained quizartinib is associated with a net population health benefit and is a cost-effective use of NHS resources (Table 86)

Additional clinical outcomes and disaggregated costs are provided in Appendix J.

Table 84. Incremental cost-effectiveness results (deterministic base-case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,851

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Table 85. Fully incremental analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER fully incremental (£/QALY)
SC regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,851
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SC, standard chemotherapy
Notes: These results are the results using the quizartinib PAS price.

Table 86. Net health benefit of quizartinib

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000 WTP threshold	NHB at £30,000 WTP threshold
Quizartinib regimen	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SC, standard chemotherapy
Notes: These results are the results using the quizartinib PAS price.

The model traces showing the proportion of patients in each of the model health states over the time horizon of the analyses are presented in Figure 46 (quizartinib), Figure 47(SC) and Figure 48 (midostaurin).

Figure 46. Patient distribution over time – quizartinib regimen

Abbreviations: CR1, first complete remission; CR2, second complete remission; HSCT, hematopoietic stem cell transplant; R/R, relapsed/refractory; 1L, first line; 2L, second line.

Figure 47. Patient distribution over time – midostaurin regimen

Abbreviations: CR1, first complete remission; CR2, second complete remission; HSCT, hematopoietic stem cell transplant; R/R, relapsed/refractory; 1L, first line; 2L, second line.

Figure 48. Patient distribution over time – SC regimen

Abbreviations: CR1, first complete remission; CR2, second complete remission; HSCT, hematopoietic stem cell transplant; R/R, relapsed/refractory; 1L, first line; 2L, second line.

B.3.9 Exploring uncertainty

B.3.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterised using probability distributions and analysed using a Monte Carlo simulation (5,000 iterations). For each PSA iteration, a new set of input parameter values was randomly sampled assuming the probability distributions specified (detailed in Table 82).

An overview of the probabilistic base case results for the cost effectiveness is shown in Table 87. Cost savings in the quizartinib regimen of [redacted] compared to the midostaurin regimen and additional costs of [redacted] compared to the SC regimens were observed. Use of the quizartinib regimen resulted in additional QALYs of [redacted] and [redacted] vs. midostaurin and SC respectively. Quizartinib was found to be dominant compared to midostaurin and an ICER of £15,712/QALY gained vs. SC was identified.

The fully incremental analyses also showed consistent results with the deterministic base case. Use of the quizartinib regimen resulted in an additional [redacted] QALYs and [redacted] LYs compared with SC and use of the midostaurin regimen as in the base case resulted in [redacted] less QALYs and [redacted] less LYs than quizartinib. The additional QALYs for quizartinib over SC were associated with an incremental cost of [redacted] whilst the loss in QALYs with the midostaurin regimen over the quizartinib regimen still resulted in a [redacted] incremental cost.

The net health benefit assessment was in line with the base case with a positive net health benefit at a WTP of £30,000/QALY (Table 88).

The PSA scatterplot is shown in Figure 49. The analyses show that the vast majority of simulations predict that quizartinib is more effective and more costly than SC. The majority of simulations also predict that quizartinib is likely either more effective and more costly than midostaurin or that quizartinib is less costly and more effective than midostaurin (i.e. dominant). Figure 50 shows a multi-way cost-effectiveness acceptability curve for the quizartinib regimen vs. the midostaurin and SC regimens. The probability of quizartinib being cost-effective at a WTP threshold of £30,000/QALY gained was 93.6%.

Table 87. Probabilistic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,712

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Table 88. Probabilistic fully incremental analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER fully incremental (£/QALY)
SC regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,712
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

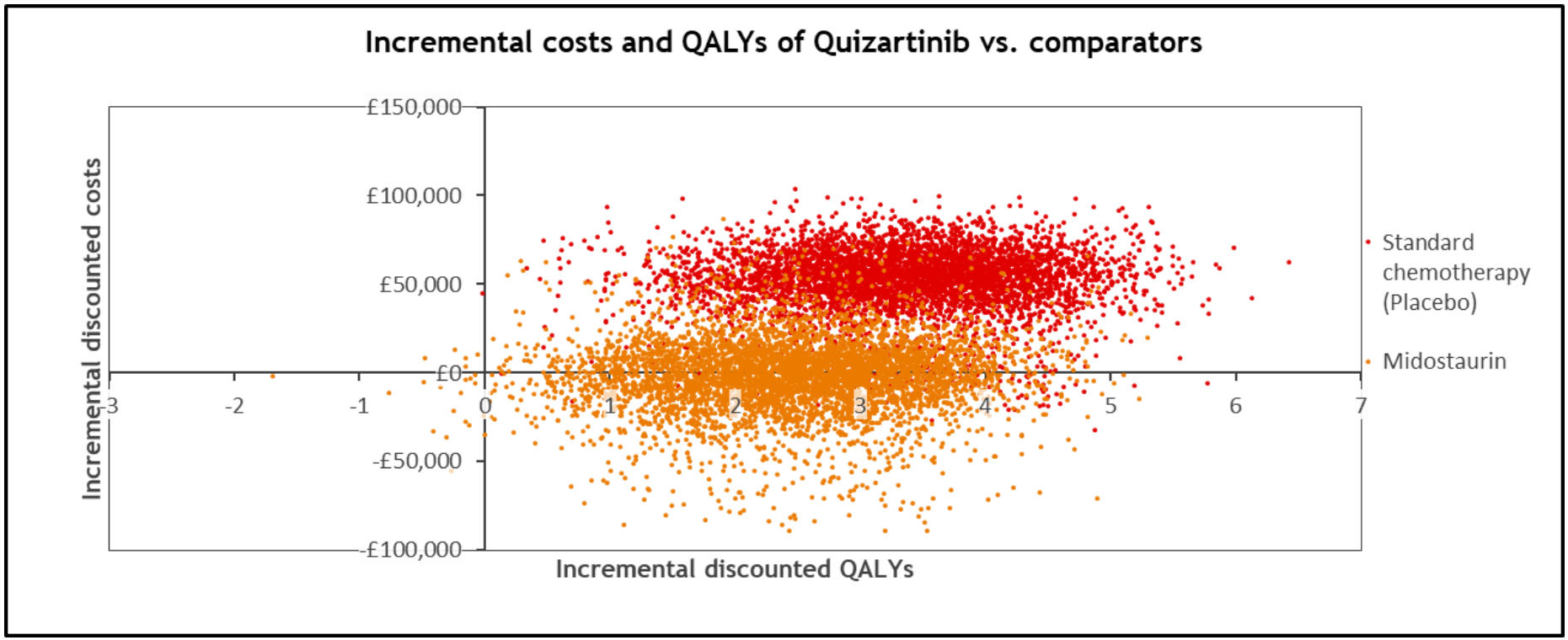
Abbreviations: LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Table 89. Probabilistic base-case net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000 WTP threshold	NHB at £30,000 WTP threshold
Quizartinib regimen	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

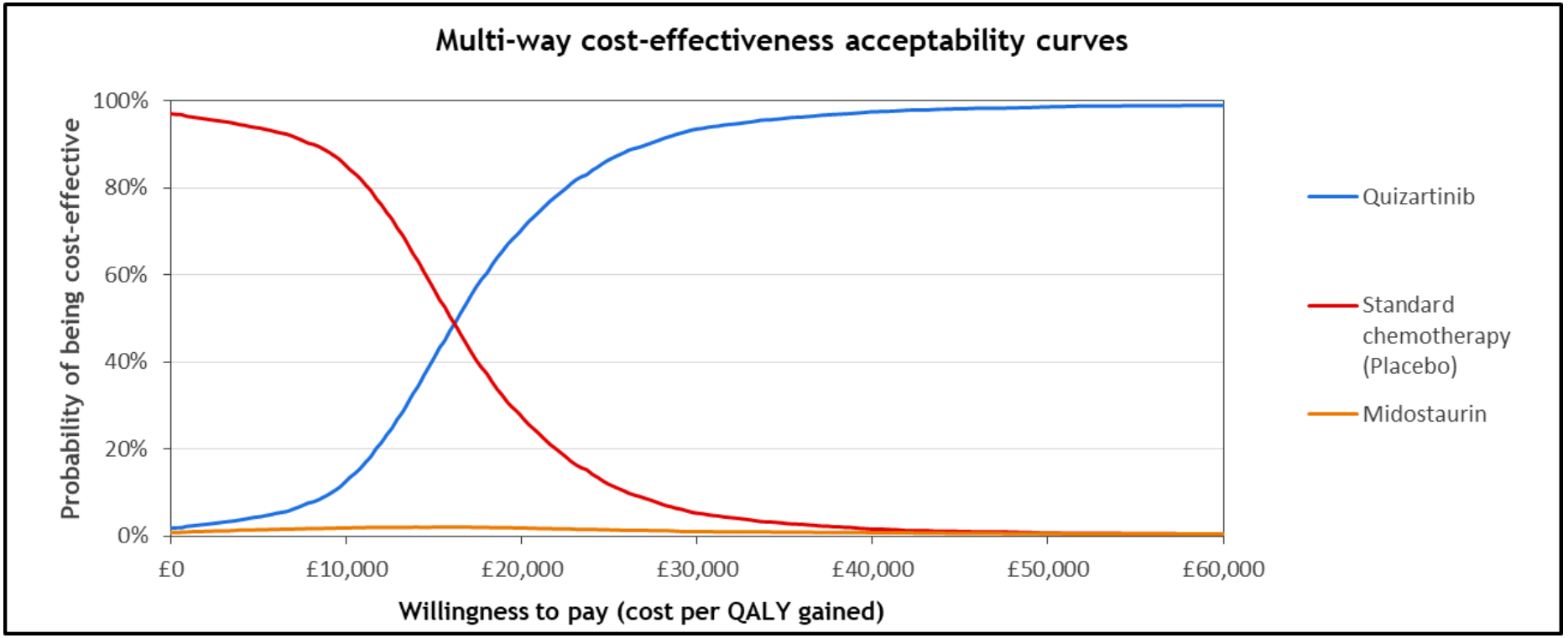
Abbreviations: LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Figure 49. Cost-effectiveness plane



Abbreviations: QALYs, quality-adjusted life years.
Notes: These results are the results using the quizartinib PAS price

Figure 50. Multi-way cost-effectiveness acceptability curve



Abbreviations: QALY, quality-adjusted life year.
Notes: These results are the results using the quizartinib PAS price

B.3.9.2 Deterministic sensitivity analysis

The robustness of the model was tested by a set of deterministic sensitivity analyses (DSAs). One parameter or model assumption was varied at a time while the other parameters were kept at base case values. Table 90 and Table 91 summarise the top 20 DSA results based on their impact on the ICER for quizartinib vs. midostaurin and SC. DSA results are also presented in tornado diagrams (Figure 51 and Figure 52).

Results of both comparisons are most sensitive to the relative treatment effect of quizartinib vs midostaurin and SC in relapse after CRc (i.e. CIR HRs from MAIC) and parameters that affect the costs of maintenance treatment with quizartinib (mean treatment duration, relative dose intensity, and proportion using maintenance after HSCT). All variations in model parameters resulted in NMBs which indicated that quizartinib was cost-effective vs. midostaurin. Similarly, all variations in model parameters resulted in ICERs below £30,000/QALY for quizartinib vs SC.

Table 90. Top 20 DSA results based on the impact on NMB (quizartinib vs. midostaurin)

Parameter	Inputs			NMB		
	Base case	Low	High	Low	High	Difference
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Abbreviations: AE, adverse event; CR, complete remission; DSA, deterministic sensitivity analysis; GVHD, graft-vs.-host disease; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; NMB, net monetary benefit; SC, Standard Chemotherapy; TP, transition probabilities; RFS; relapse-free survival.
Notes: These results are the results using the quizartinib PAS price

Figure 51. Tornado diagram (quizartinib vs midostaurin)

Abbreviations: AE, adverse event; CR, complete remission; DSA, deterministic sensitivity analysis; GVHD, graft-vs.-host disease; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; ICUR, incremental cost-utility ratio; NMB, net monetary benefit; RFS; relapse-free survival.
Notes: These results are the results using the quizartinib PAS price

Table 91. Top 20 DSA results based on the impact on the ICER (quizartinib vs. SC)

Parameter	Inputs			ICER		
	Base case	Low	High	Low	High	Difference
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Abbreviations: AE, adverse event; CR, complete remission; DSA, deterministic sensitivity analysis; GVHD, graft-vs.-host disease; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; NMB, net monetary benefit; RFS; relapse-free survival; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Figure 52. Tornado diagram (quizartinib vs. SC)

Abbreviations: AE, adverse event; CR, complete remission; DSA, deterministic sensitivity analysis; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; ICUR, incremental cost-utility ratio.
Notes: These results are the results using the quizartinib PAS price

B.3.9.3 Scenario analysis

Scenario analyses were conducted to test how changes in the model assumptions and input values derived from alternative data sources impact model outcomes. Descriptions of the scenario analyses are provided in Table 92.

Table 92. Model scenario analysis inputs

Scenarios		Base-case input	Scenario analysis input
Effectiveness based on alternative parametric functions for quizartinib			
1 to 6	Relapse from CRc	Survival model log-normal	Log-logistic, Exponential, Weibull, Gompertz, gamma, generalised gamma
7 to 11	Death from CRc	Survival model log-normal	Log-logistic, Exponential, Weibull, gamma, generalised gamma
12 to 17	Death from protocol-specified HSCT (1L)	Survival model log-normal	Log-logistic, Exponential, Weibull, Gompertz, gamma, generalised gamma
Midostaurin AE rate set equal to the quizartinib AE rate			
18	Midostaurin AE rate	Sourced from the RATIFY study	Assumed equal to the quizartinib AE rate
Alternative cure point			
19	Cure point	3 years	5 years
20	Cure point	3 years	2 years
Comparative efficacy			
21	Death from CRc, for midostaurin	MAIC conducted survival after CRc HR = 0.82 (quizartinib vs midostaurin)	Assume quizartinib and midostaurin has same efficacy in survival after CRc (i.e. survival after CRc HR = 1)
22	Trial based comparison	MAIC – quizartinib vs SC vs midostaurin	QuANTUM-First trial data – quizartinib vs SC
23	ITC approach	MAIC – adjusted population	ML-NML – unadjusted QuANTUM-First population
Death post-HSCT			
24	Death and relapse post-HSCT, for midostaurin	Assumed the same as SC	Assumed the same as quizartinib with sorafenib costs

Abbreviations: AE, adverse event; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; PAS, patient access scheme; TP, transition probability.

The results of the scenario analyses are provided in Table 93.

Table 93. Scenario analyses results

Scenario	Description		vs. midostaurin			vs. SC		
			Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
Base case	N/A		[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,851
1	Alternative parametric functions for relapse from CRc curve for quizartinib	Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,165
2		Exponential	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,445
3		Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,388
4		Gompertz	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,103
5		Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,415
6		Gen gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,814
7	Alternative parametric functions for death from CRc for quizartinib	Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,967
8		Exponential	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,619
9		Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,993
10		Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£16,011
11		Gen gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,510
12	Death from protocol specified HSCT 1L	Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,874
13		Exponential	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,725
14		Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,893
15		Log-normal	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,859
16		Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,900
17		Gen gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,971
18	Midostaurin AE rate set equal to the quizartinib AE rate		[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,851
19	Alternative cure point	5 years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£17,241
20		2 years	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,895
21	Survival after CRc for midostaurin		[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,851
22	Trial based comparison		[redacted]	[redacted]	-	[redacted]	[redacted]	£48,017
23	ML-NMR		[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£29,865
24	Survival and relapse after transplant for midostaurin		[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£15,851

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; Gen gamma, generalised gamma; OS, overall survival; QALYs, quality-adjusted life years; RFS, relapse-free survival; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Effectiveness based on alternative parametric functions for quizartinib (Scenarios 1 to 17)

Scenarios 1 to 17 explore the uncertainty related to the different parametric functions used to extrapolate relapse and death after CRc and death from HSCT. In these scenarios, 6 alternative parametric functions were tested for relapse from CRc and death from HSCT. For the death from CRc endpoint, the Gompertz curve did not converge, hence only 5 alternative models were tested.

These scenarios resulted in small variations from the base case results with quizartinib being dominant vs midostaurin in all cases and ICERs varying from £15,510/QALY gained to £16,619/QALY gained vs. SC.

The results show that the model is not sensitive to the baseline survival curves used for quizartinib. The low sensitivity of the model outcomes despite the wide variations in the different parametric models (particularly for the death from CRc and HSCT curves) are due to the assumption of functional cure after 3 years. This restricts the time frame in which the parametric models are applied, since SMR adjusted general population mortality is used after the cure point.

Midostaurin AE rate set equal to the quizartinib AE rate (Scenario 18)

The AE rate observed in the RATIFY trial was far higher than the AE rate observed in QuANTUM-First. No clear rationale for this discrepancy was identified. Hence, in scenario 3 the midostaurin AE rate was revised in line with the AE rate for quizartinib in QuANTUM-First to review the sensitivity of the model to this variable. The results showed that quizartinib is dominant vs. midostaurin which is in line with the base case. Hence, the increased midostaurin AE rates used in the base case are not a key driver of the model outcomes.

Alternative cure point (Scenarios 19 and 20)

In previous NICE submissions (TA523 (6) and TA642 (101)) a cure point of three years was accepted. This was also in line with clinical expert opinion and so was selected as the cure point for the base case. However, a two-year cure point was also considered plausible in TA642 and in TA523 clinical experts stated that they would expect that anyone whose disease was still in remission after 5 years to be cured. As a result, a scenario analysis was conducted to test the model's sensitivity to the time

point assumed for cure. The analysis of quizartinib vs. midostaurin indicated that quizartinib was dominant compared to midostaurin at both alternative cure points in line with the base case. In the comparison of quizartinib vs. SC, a cure point of two years resulted in a very similar ICER compared to the base case and a cure point of five years resulted in a slightly higher ICER compared to the base case.

Comparative efficacy (Scenarios 21 to 23)

As described in section B.3.3.3.2, the definitions of survival were not fully aligned between the MAIC and the model, since the MAIC HR is based on the OS endpoint (i.e. from randomisation) and the model applies survival from CRc. To test the sensitivity of the model outcomes to the assumed survival benefit of quizartinib over midostaurin, Scenario 21 assumes the same death from CRc for both treatments. The results showed that quizartinib remained dominant vs. midostaurin in line with the base case and for quizartinib vs. SC this resulted in no change in the ICER compared to the base case.

Detailed methods and results for scenarios 22 and 23 are provided in Appendix M. Scenario 22 describes a comparison between quizartinib and SC using QuANTUM-First data. This was not selected for the base case, as it does not allow a comparison with a key comparator (midostaurin). The trial-based comparison resulted in an ICER of £48,017/QALY for quizartinib vs SC. The increase in the ICER is due to a sharp decline in the incremental QALYs compared with the base case (mainly due to older baseline age and lower treatment effect in relapse after CRc compared to the adjusted QuANTUM-First population and MAIC outputs).

Scenario 23 explores the application of an alternative method of indirect treatment comparison. The limitations of the method are described in section B.2.8.7. The ML-NMR based comparison indicated that quizartinib was again dominant vs. midostaurin and resulted in a moderately higher ICER vs SC as compared with the base case. Hence, the model outcomes are relatively consistent across both ITC approaches.

Survival and relapse after transplant for midostaurin (Scenario 24)

In the absence of comparative efficacy estimates, for the base case analyses it was assumed that midostaurin survival post HSCT was equivalent to the SC arm of the QuANTUM-First trial. Considering patients did not receive maintenance treatment in

the RATIFY trial (and no other therapies are reimbursed as a maintenance therapy post HSCT), this was deemed the most plausible approach for the base case. However, there is some uncertainty associated with this assumption. In addition, clinical experts indicated that sorafenib could be used in patients after midostaurin induction and HSCT. To test the impact of the base case assumption in the model outcomes, a scenario was conducted, assuming equivalent survival and relapse post HSCT for quizartinib and midostaurin. This scenario also included the costs of sorafenib maintenance treatment for the midostaurin arm. This scenario again indicated that quizartinib was dominant compared to midostaurin.

B.3.10 Subgroup analysis

No subgroup analyses were conducted.

B.3.11 Validation

B.3.11.1 Validation of cost-effectiveness analysis

B.3.11.2 Technical quality control of the cost effectiveness model

A check of internal validity was performed by the model developers using a quality control process. This involved checks on the selection and results of different modelling options, calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically.

The quality check explored the following general aspects of the model:

- Top-down tests. This involved systematic variation of the model input parameters to establish whether changes in inputs results in predictable changes in the model outputs. These tests were designed to identify failures in model logic or material computation errors.

- Model internal functionality (e.g. testing of all key model parameters, extreme value testing). The following aspects of the spreadsheet were identified as key areas for detailed checking: Markov traces; translation of drug prices, AEs and resource use into state costs.
- Internal consistency. Accuracy of input data. This was checked by comparing the model inputs in Excel against the data sources referenced.

Overall, the validation identified no issues with the computational accuracy of the model.

B.3.11.3 External validation of cost-effectiveness analysis

Model inputs and assumptions were validated during an interview with two practicing UK based haematologists and three senior health economics and outcomes research (HEOR) experts conducted in October 2023 (12). The clinicians confirmed that the model structure was representative of the clinical scenarios/disease pathway and recommended a cure modelling approach was incorporated with a cure point at three years. The clinical experts also validated other key inputs including the second line treatment distribution, the mean treatment duration of midostaurin and time invariant TPs (12). As stated in section B.3.1 no other cost-effectiveness analyses of quizartinib versus SC or midostaurin were identified in the systematic search. However, previous quantification for the comparison of midostaurin versus SC was identified. The manufacturing company's base case estimate of the ICER of this pairwise comparison in the NICE TA523 was £34,327 per QALY gained. However, this was calculated with an undisclosed treatment price, QALY, and cost estimates (6). A subsequent manufacturer sponsored publication of cost-effectiveness in the UK setting estimated an ICER of £36,826 per QALY, based on 1.47 QALYs gained and an incremental cost of £54,072, but whether the public listed price or confidential discounted price of midostaurin was used was not reported. In any case, the reported QALY gain of midostaurin versus SC of [redacted] compares to [redacted] in this analysis.

B.3.12 Interpretation and conclusions of economic evidence

This submission demonstrates the cost effectiveness of quizartinib regimen as compared with midostaurin regimen and SC regimen for the treatment of newly diagnosed *FLT3-ITD*+ AML. The analysis indicates that quizartinib is dominant (i.e.

less costly and more effective) compared to midostaurin and more costly but more effective compared to placebo with an ICER of £15,851/QALY gained.

The probabilistic base case results indicated that quizartinib was dominant compared to midostaurin which was in line with the base case. The results indicated a slightly lower ICER for quizartinib vs. SC compared to the base case (ICER versus SC: £15,712/QALY gained). Quizartinib remained cost-effective in the PSA with a 93.6% likelihood of quizartinib being cost-effective at a willingness to pay threshold of £30,000/QALY gained.

The DSA results indicated that quizartinib remained a cost-effective treatment option when multiple parameters were varied. The scenario analyses further highlighted the robustness of the base-case results. The difference in incremental QALYs (vs SC) between the base case and direct pairwise comparison is acknowledged. The base case applied the HR from the MAIC for midostaurin and SC, using the adjusted QuANTUM-First quizartinib arm as reference, while the direct comparison used unadjusted QuANTUM-First trial data. The model was designed to reflect UK clinical practice as per the ELN guidelines for the management of *FLT3-ITD*+ AML. Both the modelled treatment pathway and the clinical data underpinning the results are aligned with these treatment recommendations.

The main strengths of the economic assessment are:

- The model structure captures patients' responses to both 1L and 2L therapy (which was a criticism of TA523) and clinical experts confirmed the structure was representative of the clinical scenarios/disease pathway.
- The clinical trial on which this economic model is based (QuANTUM-First) was robust and well conducted in patient's representative of the population expected to be treated for newly diagnosed *FLT3-ITD*+ AML in the UK.
- Several alternative scenarios are presented allowing for the assessment of uncertainty, including alternative parametric functions, sources to inform efficacy and safety inputs, and method of estimating relative treatment effect.

The main limitations of the economic assessment are:

- The RATIFY trial which was used to derive efficacy data for midostaurin was conducted in a population with a more restricted age group (RATIFY: 18-59 years old; QuANTUM-first: 18-75 years old) (10, 21). To account for this, only data from patients aged under 60 years from the QuANTUM-First population weighted for the RATIFY population were used in the model base case – the decision problem population was therefore an adjustment of the QuANTUM-First ITT population.
- Published literature of the RATIFY trial for *FLT3-ITD* population were limited to aggregated outcomes (84). For use in a state transition model with intercurrent events (such as complete remission and HSCT), assumptions were necessarily required for the estimate of relative treatment effects. Furthermore, the RATIFY trial did not report on the composite CRc outcome, which is a recognised marker of response to therapy in UK clinical practice. Again, this required an assumption of transposition of endpoints, albeit low-risk given post-hoc examination of trends within QuANTUM-First trail results.
- Information to derive TPs from the health states following failure of 1L treatment was not available in the QuANTUM-First trial nor in the RATIFY trial as they enrolled newly diagnosed patients and had limited follow up time to evaluate outcomes in the next treatment line. As such, data to inform these TPs were sourced from the literature, namely publications on the ADMIRAL trial (111, 112).

In summary, quizartinib is a novel oral, once-daily targeted therapy that can provide an innovative treatment option for eligible patients with newly diagnosed *FLT3-ITD*+ AML and represents a cost-effective use of UK NHS resources compared with current standard of care.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Summary of Information for Patients (SIP)

March 2024

File name	Version	Contains confidential information	Date
ID4042_quizartinib_SIP_v1.0	**1.0**	**No**	**7th March 2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International - Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Quizartinib

Brand name: VANFLYTA®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Adults who have acute myeloid leukaemia (AML, a type of blood cancer), with a mutation in the FLT3 gene called '*FLT3-ITD*' (a genetic change that usually occurs in AML).

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Quizartinib was granted an authorisation to be marketed in the European Union in 6th November 2023 (1). A marketing authorisation application for quizartinib was also submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA) - the government agency that is responsible for regulating medicines in the UK - on the 22nd of September 2023 and a decision is expected within the second quarter of 2024.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

At the time of submission, Daiichi Sankyo UK does not have any collaborations with any leukaemia patient groups in the UK nor has it provided financial support to any such groups.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is acute myeloid leukaemia?

AML is a cancer of the blood and bone marrow, the inner part of the bones that produces new blood cells (2, 3). The bone marrow produces two types of immature cells (myeloid stem cells and lymphoid stem cells). Myeloid stem cells turn into three types of mature cells over time, which will carry oxygen (red blood cells), fight infections (white blood cells) and stop bleeding (platelets) (2). In AML, the body produces a large quantity of abnormal white blood cells that do not follow the usual process to become healthy mature cells (2, 4). These cells do not have the same ability as normal cells to fight infections, and their accumulation results in the reduced production of other normal blood cells (3). This means that people diagnosed with AML are more likely to get infections and have greater difficulty in getting over those infections (5). Without treatment, AML progresses rapidly and death may occur within months of diagnosis due to infection or bleeding (3).

Genetic changes, known as mutations, can cause AML, and the type of mutation can impact the severity of the disease. The FLT3 gene is commonly affected in AML, where two types of mutations can occur: *FLT3-ITD* (found in 20% to 25% of patients) and *FLT3-TKD* (in 7% to 10% of patients) (6-8). The *FLT3-ITD* mutation indicates that patients may have a worse prognosis, and is classified as having an 'intermediate risk' (9). Treatment for patients that have this mutation can target the specific mutation that is causing AML, rather than just using traditional chemotherapy which targets cell growth or reproduction more broadly.

How many people are diagnosed with AML?

AML is an aggressive cancer associated with poor survival (3), with more than 3,000 people being diagnosed in the UK every year (10, 11).

What is the impact of AML on patients' quality of life?

When compared to the general population, patients with AML usually experience lower quality of life (12, 13). UK studies have found that patients in the diagnosis, treatment and relapse (i.e. when the disease returns) stages have an especially low quality of life related to their health (14-16). Unsurprisingly, when compared to the general population, patients with AML usually experience lower health related quality of life (HRQoL) (12, 13).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The diagnosis of AML is typically made based on several tests, including blood tests, genetic analyses and an examination of the bone marrow (9). Doctors may also do other tests (such as genetic tests to search for the *FLT3-ITD* mutation) at the time of the diagnosis to help them decide which treatments will work best and to assess the disease prognosis (9, 17-19).

No additional tests are required for treatment with quizartinib.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment guidelines are available for patients with AML in the UK?

Currently the European LeukemiaNet (ELN) 2022 guidelines are the main guidelines followed for the management of AML in the UK (9). Other guidelines include the National Health Service (NHS) Pan-London guidelines and the 2020 European Society for Medical Oncology (ESMO) guidelines (18, 19).

The available guidelines recommend the use of more specific drugs - called FLT3 inhibitors - for the treatment of AML patients who have the *FLT3* mutation, in combination with chemotherapy drugs routinely used in AML patients (if these are considered healthy enough). The goal of this combined treatment is to increase its overall impact on leukaemia cells and improve patients' prognosis (9, 18, 19).

What are the current treatment options?

The recommended treatment regimens usually follows three stages: induction (aims to kill as many leukaemia cells as possible), consolidation (aims to eliminate any remaining

leukaemic cells after induction and prevent the cancer from returning, which is called relapse) and maintenance (aims to reduce the risk of relapse administering a lower dose of treatment). Patients can also be offered the option to receive a hematopoietic stem cell transplant (HSCT) (9, 20), a procedure in which a patient receives healthy stem cells with the goal of replacing their own cells that have been previously destroyed by treatment (2).

Midostaurin is the only FLT3 inhibitor drug currently recommended in the guidelines. Daunorubicin/idarubicin and cytarabine are the standard chemotherapy drugs of choice for the treatment of AML (9, 18, 19). The combination treatment recommended by the main guidelines is comprised of midostaurin + daunorubicin or idarubicin + cytarabine in induction, midostaurin + cytarabine with or without HSCT in consolidation and midostaurin alone in maintenance (9).

What are the limitations of the current treatment options?

Despite currently available treatments, there is still a need for new treatment options for AML adult patients with the *FLT3-ITD* mutation (21-24).

There is still a high chance of disease relapse and poor survival with currently available treatments (21, 25). Also, there is still no treatment that specifically targets the *FLT3-ITD* mutation (26).

Who is quizartinib recommended for?

Quizartinib is even more specific than the presently available FLT3 inhibitor (midostaurin) as it targets a subtype of *FLT3* (*FLT3-ITD*), that affects the majority of patients with a *FLT3* mutation (27). Quizartinib is expected to be positioned as a new treatment option for adult patients who are newly diagnosed with AML, have a *FLT3-ITD* mutation and are considered fit to receive an intensive chemotherapy treatment. It is intended to be administered in combination with the already existing chemotherapy treatments used in treatment of AML.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Some studies representative of patient-based evidence (PBE) about the symptoms and impact of living with AML are described below. There are ongoing efforts to generate further PBE about living with this disease, and a 2023 leukaemia patients and carers survey is currently open for patients and carers.

Global Leukaemia Experience Survey, 2023

A total of 2,646 leukaemia patients responded to a patient experience survey, from which 312 (12%) were patients with AML. AML patients reported fatigue and feeling breathless as their main symptoms prior to receiving a diagnosis. Overall, 45% of patients reported that the treatment's side effects had a small impact on their lives, and fatigue was the most commonly reported side effect (53%). The quality of life of leukaemia patients can be severely impacted, with patients commonly reporting difficult with self-care and leaving their house, as well as feeling isolated, anxious and depressed. Moreover, oral treatments were the administration route mostly requested for new treatment options (28).

The views of carers of these patients were also collected in a survey, with a total of 571 respondents, of which 110 (19%) were carers of AML patients. In this survey, 48% of carers reported that side effects had a significant impact on the patient they were caring for. In terms of quality of life, overall carers reported a higher impact on patients' quality of life than the patients themselves. 64% of carers reported a negative impact on their wellbeing and on their finances (28).

Grauman, 2023

Another study explored the perceptions of 16 AML patients by interviewing them about precision medicine (also called personalised medicine, consisting in the use of distinct characteristics, computational features and algorithms for the prediction and improvement of the patient's disease risk and treatment response) and whether they would like to be involved in this new area and in the decision-making process. Patients reported that they are in a particularly sensitive state when treatment decisions need to be taken, and that their reduced understanding of the treatment options makes it challenging to choose. Nevertheless, most patients wanted to be involved in the discussion of the available treatments' benefits and risks (29).

Tomaszewski, 2016

In this study, interviews with 23 AML patients from the United States and Japan were conducted in order to understand their experience of living with this disease. Patients were split into groups according to their disease status (e.g. relapse, after-transplant) and were then interviewed by phone and asked about their symptoms, as well as the impact that these symptoms and AML treatments have on their lives (e.g. in their day-to-day activities, work, social life) (30).

The symptoms that were most commonly reported by patients were fatigue (feeling tired), bruising, weakness, nausea (feeling sick) and headaches. In terms of the perceived impact on their daily lives, patients mostly referred a decreased ability to function and to keep their social and family roles, anxiety, and worry about the uncertainty of their remission status (absence of symptoms) (30).

Other studies exploring patients' preferences in the mode of administration of AML treatments and what is most valued in the maintenance phase of the treatment, are also available.

Delmas, 2023

Interviews with 21 AML patients in Germany, the United Kingdom and Spain were conducted, where the importance of treatment characteristics was evaluated. Most patients reported a preference for treatments administered orally (71%) since they are more convenient. Patients preferring treatments administered intravenously or subcutaneously (24%) mentioned the advantages of these acting faster and being monitored while receiving treatment (31).

Tervonen, 2020

Patients in the United States, Canada, Germany and Italy who had received treatment for AML participated in an online survey that explored the clinical benefits, side effects, mode of administration, and out-of-pocket costs of AML maintenance treatments. Results of this online survey, taken by 170 patients, revealed that an increased probability of survival at 2 years (i.e. extension of life) was the characteristic they valued the most in AML treatments in the maintenance phase. Patients also demonstrated a strong preference for an oral treatment (32).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

AML patients produce a high amount of abnormal immature white blood cells called myeloblasts (33). These abnormal cells fail to fight infection and prevent the normal blood cells from working properly (3). Quizartinib treats AML by blocking the action of some enzymes (kinases) in these abnormal cells, which reduces or stops their division process and uncontrollable growth. In addition, quizartinib helps immature cells to grow into normal ones (33). Quizartinib is a novel treatment as there are no treatment options for AML that specifically target the *FLT3-ITD* mutation.

The summary of product characteristics (SmPC) and patient information leaflet (PIL) can be downloaded here.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Quizartinib is intended to be used along with intensive chemotherapy. The most commonly used chemotherapies in the treatment of AML include daunorubicin or idarubicin and cytarabine (see section 2c for further details). The combination of quizartinib with these chemotherapies aims to maximise the effect against leukaemia cells (9).

Daunorubicin and idarubicin belong to a group of drugs called anthracyclines. Cytarabine and anthracyclines work by destroying quickly dividing cells, such as cancer cells. In this way, they prevent the cancer from growing (34, 35). Similarly, the three drugs stop cancer cells from making the genetic material (DNA) that they need to grow and multiply (35-38). The main difference between these drugs is that cytarabine also disrupts the DNA repairing process, while daunorubicin/idarubicin cause damage to the DNA itself (35-37). These treatments have long been part of clinical guidelines, are a well-established approach in the treatment of AML (39) and are expected to be routinely available in the NHS.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Quizartinib is a tablet that can be taken orally. The treatment is broken down into three phases: induction, consolidation and maintenance. In each phase, patients can receive one or more cycles of treatment, where each cycle lasts for 28 days (4).

Induction: 35.4 mg (two 17.7 mg tablets) once daily for two weeks in each cycle of induction (maximum two cycles), in combination with standard chemotherapy (4).

Consolidation (for patients with no remaining signs of disease after induction): 35.4 mg (two 17.7 mg tablets) once daily for two weeks in each consolidation cycle (maximum four cycles), in combination with standard chemotherapy) (4).

Maintenance: 26.5 mg (one tablet) once daily for two weeks, increased to 53 mg (two 26.5 mg tablets) once daily for the remaining two weeks of a treatment cycle depending on how the patients responds to quizartinib (maximum 36 cycles) (4).

Treatment with quizartinib will be initiated in the hospital by the patient's doctor (haematologist) and will be continued by patients in their home. Both quizartinib and

midostaurin are taken orally, however quizartinib is only taken once a day instead of twice (midostaurin), which will likely interfere less with patients' daily activities.

The present treatment used in *FLT3*+ AML patients (midostaurin) is administered in the same three phases alongside chemotherapy. The key differences being that midostaurin is administered twice rather than once daily, maintenance therapy of midostaurin can only be continued for up to 12 cycles and it cannot be restarted after a stem cell transplant (40).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, etc. Please provide references to further information about the trials or publications from the trials.

Quizartinib was studied in a clinical trial (QuANTUM-First), that evaluated the efficacy and safety of quizartinib and placebo (an inactive drug) in combination with standard chemotherapy in adults diagnosed with AML who had a *FLT3-ITD* mutation and were considered eligible to receive chemotherapy (27). A brief summary of QuANTUM-First is provided in the table below, and further details about the study are available here.

Study title	QuANTUM-First (27)
Study description	Eligible patients were randomly assigned to receive either quizartinib or placebo in combination with standard chemotherapy in induction and consolidation phases, then administered as a single-agent therapy in the maintenance phase for up to 36 28-day cycles
Location	Quizartinib was studied across 193 sites in 26 countries: Spain, Italy, Republic of Korea, Japan, China, US, France, Brazil, Germany, Russian Federation, Taiwan, Hungary, Czech Republic, Romania, Israel, Canada, Serbia, Poland, Portugal, Australia, Belgium, Bulgaria, Croatia, Ukraine, Singapore and the United Kingdom
Population	Adults (18 to 75 years old) with newly diagnosed AML with a *FLT3-ITD* mutation
Patient group size	Between September 2016 and August 2019, 539 patients were included in this study. Number of patients enrolled and treated with quizartinib: 268 Number of patients enrolled and treated with placebo: 271
Intervention	Quizartinib + standard chemotherapy
Comparator	Placebo + standard chemotherapy
Key inclusion and exclusion criteria	Inclusion criteria Adult patients between 18 and 75 years of age, newly diagnosed with *FLT3-ITD*+ AML at screening were enrolled in the QuANTUM-First trial. Exclusion criteria Patients with diagnosis of AML caused by previous chemotherapy or radiotherapy for other cancers or with uncontrolled or serious cardiovascular disease were excluded from the QuANTUM-First trial.
Study publication	Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with *FLT3*-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind,

	placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10388):1571-1583. doi:10.1016/S0140-6736(23)00464-6	

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Results from the QuANTUM-First study show that quizartinib is an effective treatment option for these patients, when administered along with chemotherapy (27). See section 3d) for further details on the study.

The efficacy of quizartinib was measured based on the improvement of the following indicators (41, 42):

- **Overall survival (OS)** refers to how long patients live after treatment
- **Survival rate** refers to the proportion of patients that are still alive after a specific period of time
- **Event free survival (EFS)** refers to how long patients experience an 'event' (e.g. relapse or death) after treatment
- **Complete remission (CR)** refers to no signs of cancer on scans or tests after receiving treatment
- **CR rate** refers to the proportion of patients experiencing CR after a specific period of time. Duration of CR is measured to see how long patients remain in CR

The results of this study are summarised below (4, 27):

Improvement in overall survival (OS)

Patients who had quizartinib lived for about 31.9 months (median* OS), while those who received placebo lived for about 15.1 months. Overall, patients were followed for 39.2 months (median* follow-up time).

Improvement in survival rate

The proportion of patients who remained alive (survival rate) was assessed at various timepoints and was higher for those who had quizartinib, compared with those who had placebo: 12 months (67.4% vs 57.7%), 24 months (54.7% vs 44.7%), 36 months (49.9% vs 41.1%) and 48 months (48.4% vs 37.0%).

Similar EFS

The EFS was 0.03 months in patients that received quizartinib and 0.71 months in patients that received placebo. However, these results were based on a stricter definition of what EFS means, requested by the United States authority (Food and Drug Administration [FDA]). If considering the originally intended definition of EFS, a benefit for quizartinib was observed (11.9 versus 5.7 months).

Similar CR rate

The proportion of patients experiencing CR (CR rate) in the induction phase was 54.9% for those who had quizartinib compared with 55.4% for those who received placebo.

Improvement in duration of CR

The length of time that patients remained in CR (median* duration of CR) was increased in patients who received quizartinib (38.6 months), compared to those who received placebo (12.4 months).

*Median refers to the middle value in a set of values (43)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The QuANTUM-First trial measured patients' health related quality of life (HRQoL) using the EuroQol 5 Dimension 5 Level (EQ-5D-5L) tool.

EQ-5D consists of a descriptive system comprised of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), and patients are asked to rate their health state in each of the dimensions in 1 of 5 levels (from no problems to extreme problems) (44). EQ-5D is the tool preferred by NICE to measure the health-related quality of life (HRQoL) in adults (45).

Results from the EQ-5D-5L questionnaire were similar between quizartinib and placebo. The differences in these scores over the time period patients were followed was below the smallest improvement deemed significant by a patient (27) (minimal clinically important difference [MCID] (46)), which suggests that the addition of quizartinib to the standard chemotherapy treatment does not lead to a negative impact on patients' quality of life.

Further details on HRQoL results are described in Document B of the company evidence submission.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient

readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Overall, quizartinib has been shown to be a generally well tolerated treatment option, similarly to what is expected in AML patients receiving the currently available treatments (21, 27).

Like all medicines, quizartinib can cause side effects, although not all patients experience them (33). The most common side effects (recorded in ≥10% of patients) generally occurred with similar frequencies in both study groups (quizartinib and placebo) (27). The most common side effects (which may affect more than 1 in 10 people) were increase in alanine aminotransferase (abnormal liver enzyme results), thrombocytopenia (low levels of blood platelets), anaemia (low levels of red blood cells), neutropenia (low levels of neutrophils, a type of white blood cell), diarrhoea, nausea (feeling sick), abdominal (stomach) pain, headache, vomiting, oedema (swelling of the face, arms and legs), upper respiratory tract infections (nose and throat infections), decreased appetite, epistaxis (severe nosebleeds), fungal infections, herpes infections, dyspepsia (indigestion) and bacteraemia (bacteria in the blood) (33).

Patients should contact their healthcare professional if they experience one of the following serious side effects:

- feeling dizzy, lightheaded or faint, which could be signs of a heart problem called 'prolonged QT interval' (abnormal electrical activity of the heart that affects its rhythm)
- fever, cough, chest pain, shortness of breath, tiredness or pain when urinating. These could be signs of an infection or febrile neutropenia (low white blood cell counts with fever)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

- Quizartinib is an oral, second-generation medicine belonging to a class of drugs called FLT3 inhibitors - which specifically acts on the *FLT3-ITD* mutation - and has manageable side effects (27)
- The QuANTUM-First study assessing the effects of quizartinib was the first randomised study that included AML patients with the *FLT3-ITD* mutation only who were eligible for treatment with intensive chemotherapy. This study also included elderly subjects, for whom there are still even more limited treatment options (27)
- Quizartinib is administered orally once a day, while the currently available FLT3 inhibitor midostaurin requires an oral administration twice a day (21, 27)
- Quizartinib dosing scheme fits into patients' schedules, without interrupting their daily activities
- Quizartinib reduced the risk of death by 22.4% versus placebo (27)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Key disadvantages of the treatment with quizartinib are outlined below (33):

- **Blood tests**

Regular blood tests are required during treatment with quizartinib to check the patient's blood cells (white blood cells, red blood cells and platelets) and electrolytes (salts in the blood, such as sodium, potassium, magnesium, calcium, chloride and bicarbonate)

- **Electrocardiogram**

An electrocardiogram (ECG) will be performed before and during treatment to check if the patient's heart is beating normally. This will be done more often if the patient is taking other medicines that prolong the QT interval (which may further increase the risk of QT prolongation, one of the serious side effects that may occur during treatment)

- **Infections in patients older than 65 years**

Elderly patients have a higher risk for serious infections, especially in the initial treatment period. Patients older than 65 years old will be more closely monitored for the occurrence of serious infections.

- **Other medicines**

Some medicines may affect how quizartinib works, either by increasing the risk of side effects due to increased levels of quizartinib in the blood, reducing its effectiveness or increasing the risk of QT prolongation. See the PIL for more detailed information on which medicines can affect how quizartinib works.

- **Pregnancy**

Patients should not receive treatment with quizartinib during pregnancy, as it may harm the unborn baby.

- **Breast-feeding**

Patients should not breast-feed during treatment with quizartinib, as well as for at least 5 weeks after stopping treatment.

- **Fertility**

Quizartinib may reduce fertility in women and men.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and

issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a health economic model. The pharmaceutical company uses the health economic model to perform an analysis which compares the costs and benefits of the new treatment (quizartinib + standard chemotherapy) with the currently available treatments, referred to as comparators.

The model reflects AML patients with the *FLT3-ITD* mutation

A cost-effectiveness model - a type of economic analysis that assesses the effectiveness of selected treatments in relation to their cost (47) - informed by a literature review of previously published cost-effectiveness studies in *FLT3*+ AML patients was developed, in order to capture the costs and benefits on introducing quizartinib in the current treatment pathway. Therefore, the developed model compared quizartinib + standard chemotherapy with the currently available treatments for adults with *FLT3*+ AML (midostaurin + standard chemotherapy and standard chemotherapy alone). The economic model simulates several health states (e.g. induction, complete remission, relapse) that aim to reflect the path of patients with AML in real life.

The model reflects how much treatment with quizartinib may impact patients' lives

The economic model developed for quizartinib uses data from the QuANTUM-First study and from an indirect treatment comparison analysis - a method used to indirectly compare two treatments when studies that directly compare the drugs of interest are not available (47) - comparing the efficacy of quizartinib and midostaurin to simulate the pathway of AML patients with the *FLT3-ITD* mutation over their lifetime. Since data from the clinical study is not available for this entire time horizon (patients in the QuANTUM-First study were followed for 39.2 months on average (27)), a set of statistical tests was applied to extrapolate the available data in order to reflect the remaining lifetime of these patients in the model.

The model reflects the impact of treatments in patient's quality of life

The model is also programmed to reflect the impact that the selected treatments (quizartinib, midostaurin and standard chemotherapy regimens) have on patients' qualify of life.

As described in section 3f), patients' quality of life was assessed in the QuANTUM-First study using the EQ-5D-5L tool. However, it was noted that these data had some inconsistencies and therefore data from published literature was used to inform the model instead. A literature review was conducted to best inform which quality of life data should be used in the model.

The model reflects the costs related with the treatment with quizartinib and with the selected comparators

The model captures costs that directly affect NHS resources, such as costs with drug acquisition, drug administration (e.g. for intravenous drugs), tests and procedures to monitor patients' disease status, management of side effects and stem cell transplant.

Quizartinib is expected to lead to additional costs of acquiring the drug. Since it is administered orally, similarly to the currently available drug midostaurin, no additional administration costs are expected with the introduction of quizartinib in the treatment pathway.

Model uncertainties were explored

Additional analyses have been conducted to investigate the sensitivity of the model results and to what extent some of the parameters used can impact the model results. Additionally, scenarios considering alternative data were used to investigate its impact on the final results. This allows decision makers to understand how robust the model results are, providing additional evidence that best supports them in making an informed decision regarding the adoption of quizartinib in the NHS.

What do results of the cost-effectiveness analysis tell us?

Results of the cost-effectiveness model demonstrate that treatment with quizartinib is a cost-effective use of NHS resources in adult patients that are newly diagnosed with AML, have a *FLT3-ITD* mutation and are considered fit to receive an intensive chemotherapy treatment.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Quizartinib is a novel drug belonging to a class of drugs called FLT3 inhibitors that specifically targets a subtype of the *FLT3* mutation (*FLT3-ITD*) (27).

Quizartinib requires a once-daily dosing scheme, fitting into patients' schedules without interrupting their daily activities (27)

Quizartinib can be used in the maintenance phase, even after patients receive a stem cell transplant (27).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues were identified in relation to quizartinib.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• European LeukemiaNet guidelines (2022): https://ashpublications.org/blood/article/140/12/1345/485817/Diagnosis-and-management-of-AML-in-adults-2022 • NHS - AML: https://www.nhs.uk/conditions/acute-myeloid-leukaemia/ • Publication of QuANTUM-First study: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00464-6/fulltext Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA - Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Acute myeloid leukaemia (AML)**: a type of blood cancer where the bone marrow makes too many immature blood cells that are not able to function properly (5).
- **Bone marrow**: the spongy tissue in the centre of some bones that makes blood cells (48).
- **Blood count**: a blood test that shows the number of different types of blood cell in the blood (48).
- **Chemotherapy**: a type of cancer treatment that aims to prevent cancer from growing by killing quickly dividing cells (49).
- **Consolidation**: the second phase of treatment course for AML that aims to kill all remaining cancer cells to avoid the cancer coming back (20).
- **EuroQol 5 Dimension (EQ-5D)**: a widely used instrument evaluating quality of life.
- ***FLT3* mutation**: the *FLT3* of '*FLT3* mutation' refers to the *FLT3* gene, which is responsible for the production of a protein called FMS-like tyrosine kinase 3 (the FLT3 protein). This protein manages the growth and division of some cells. The change to the *FLT3* gene, called *FLT3* mutation, affects the function of the FLT3 protein (50).
- **Hematopoietic stem cell transplant (HSCT)**: part of cancer treatment where stem cells are collected in advance and put back to the human body after killing cancer cells. This treatment helps re-establish blood cell production in AML patients (51, 52).
- ***Internal* tandem duplication (*ITD*)** and **tyrosine kinase domain (*TKD*)**: *FLT3* mutation is categorised into different subtypes. *ITD* and *TKD* are two subtypes of *FLT3* mutation (6).
- **Induction**: the first phase of treatment course for AML that aims to kill as many cancer cells as possible (20).
- **Maintenance**: the third phase of treatment course for AML given over a long period of time that aims to prevent the cancer from coming back as long as possible (53).
- **Prognosis**: estimation for whether the cancer is possible to be cured or what is likely to happen in the future (54).
- **Targeted drugs**: medicines treating cancers by altering the signals that help cancer cells survive or grow (55, 56).
- **Quality of life**: a concept to measure how people enjoy their lives. In clinical trials, quality of life reported by patients is collected to assess the positive and negative effects of treatment on their wellbeing (57).
- **Radiotherapy**: a type of cancer treatment that uses radiation to kill cancer cells (58).
- **Relapse**: the return of cancer (59).
- **Stage**: a classification system that describes the severity of cancer. The later the stage is, the more severe the cancer is (60).

- **Stem cells**: special cells made by bone marrow that are able to become different types of blood cells (61).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]
Clarification questions

May 2024

File name	Version	Contains confidential information	Date
Quizartinib EAG clarification questions	**1.0**	**Yes**	**10/05/2024**

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

QuANTUM-First Trial

A1. Priority Question: The latest data cut-off for QuANTUM-First is 13/08/21. Please confirm if any additional more recent outcome data are available.

A1 Response: The latest efficacy data (data cut-off [DCO] date of 13 Aug 2021) has been used in the submission and no further data is expected for QuANTUM-First.

The final and cumulative safety data for QuANTUM-First is available with a DCO date of 16 Jun 2023. There are safety data on 32 patients in the quizartinib arm and 26 in the placebo arm who continued past the August 2021 DCO and their safety profile was consistent with the original Clinical Study Report (CSR). An addendum to the CSR is submitted together with these responses.

A2. Priority Question: Appendix E (subgroup analyses, Figure 1) shows that overall survival (OS) for individuals with confirmed mutated Nucleophosmin 1 (NPM1) was statistically significantly superior in the quizartinib arm compared with placebo, whereas no difference between the trial arms was found for individuals with no confirmed *NPM1* mutation. Clinical advice to the evidence assessment group (EAG) found this result surprising given that, as stated in

Appendix E (p.8) the *NPM1* mutation's favourable prognosis is limited to a subset of individuals without a FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutation. Please comment on this subgroup analysis, with any clinical explanation as appropriate.

A2 Response: Although the study was not designed to assess the impact of nucleophosmin 1 (NPM1) mutation status on treatment outcomes, the results seen in the mutant NPM1 (NPM1mut) and WT NPM1 (NPM1wt) subgroups are consistent with the event free survival (EFS) and complete remission (CR)/composite complete remission (CRc) analyses in the overall study population. Consistent with the well-established role of NPM1 wild type (wt) as an adverse prognostic factor (1, 2) better outcomes were observed in NPM1 mutation (mut) subjects compared to NPM1wt subjects, including the longer median EFS based on the primary and two sensitivity EFS analyses, as well as the higher rates of CR and CRc in NPM1mut subjects versus NPM1wt subjects. No differences were seen when comparing the rates of CR or CRc for quizartinib and placebo in both the NPM1mut and NPM1wt subgroups, which is consistent with the results seen in the overall population. Similarly, when comparing the treatment effect of quizartinib versus placebo based on EFS in both the NPM1mut and NPM1wt subgroups the results are consistent with the trends in the overall population. When considering the protocol-defined EFS based on induction treatment failure (ITF) as not achieving CRc by the end of the Induction Phase, hazard ratios (HRs) of 0.760 in the NPM1wt subgroup and 0.696 in the NPM1mut subgroup were observed, suggesting there may be a benefit of quizartinib in both NPM1 subgroups. It is important to recognise the high unmet medical need in the high-risk FMS like tyrosine kinase 3 internal tandem duplication positive (FLT3-ITD+) NPM1wt population where treatment outcomes associated with available therapies remain unsatisfactory. This result also agrees with the recent 2022 European Leukemia Network (ELN) risk groups that place all NPM1 mutant patients with FLT3-ITD in the intermediate risk group.

A3. Priority Question: We understand that exploratory subgroup analyses in individuals undergoing maintenance therapy in QuANTUM-First were reviewed by the Food and Drug Administration (FDA). The prescribing information for quizartinib (p.17) reports that: in the 43% of patients (89/208) who received maintenance therapy with quizartinib or placebo after consolidation

chemotherapy, the OS hazard ratio (HR) was 0.40 (95% confidence intervals [CI]: 0.19-0.84). In the 57% of patients (119/208) who underwent maintenance therapy with quizartinib or placebo following haematopoietic stem cell transplant (HSCT), the OS HR was 1.62 (95% CI: 0.62-4.22).(3)

a. **Please describe the methodology used to produce these estimates, including any adjustments.**

b. **Please present a table showing the comparability of patient characteristics at the time of maintenance therapy among those who underwent maintenance therapy in the quizartinib and placebo groups for each of these two subgroup analyses.**

c. **Where applicable, please provide additional subgroup analyses with (Kaplan-Meier [KM] curves and HR with 95% CI) for individuals who underwent maintenance therapy, using a Cox Regression model with adjustment for any differences in participant characteristics from the time of initiating maintenance therapy, for the following outcomes: OS, and cumulative incidence of relapse (CIR). Please provide results separately for individuals who underwent HSCT and those who did not undergo HSCT.**

A3a Response: As requested by US FDA, subgroup analyses of OS were performed on the subjects who entered maintenance therapy by HSCT status prior to the maintenance phase (4). The subgroup analysis includes only subjects entering the maintenance phase of the study (N=208, where 116 in quizartinib and 92 in placebo arm).

Overall survival (OS) was analysed from randomization for the two subgroups of subjects with or without HSCT, and the HR with 95% confidence interval (CI) was estimated using unstratified Cox regression.

The results of analysis of OS for subjects who entered maintenance phase by HSCT Status (intention to treat (ITT) Analysis Set) were presented in Table 1, where the OS rates at 12, 24, 36, and 48 months were also provided.

The median OS (95% CI) was not reached in either treatment arm in the group of subjects with HSCT prior to maintenance (HR [95% CI]: 1.62 [0.62, 4.22]). There are

only a small number of death events (20 events in total) observed in all subjects who entered the maintenance phase after prior HSCT (Table 1). As a result, the 95% CI for the HR of quizartinib versus placebo is very wide (0.623 to 4.220), making it difficult to draw definitive conclusions.

The Kaplan-Meier (KM) curves of the two treatment arms in subjects with HSCT prior to maintenance overlap in the first 24 months (Figure 1). After 24 months, considerable censoring occurred due to a minimum follow-up for the primary outcome was 24-months since the time of the last subject randomised. This introduces additional uncertainty and limits the interpretation of the results thereafter.

In the group of subjects without HSCT prior to maintenance, the median OS (95% CI) was not reached in the quizartinib arm and was 42.5 (20.5, not estimable (NE)) months in the placebo arm with an HR [95% CI]: 0.401 [0.192, 0.838]; (Table 1). There appears to be a clear separation of the two KM curves between the two treatments arms in the subjects without HSCT prior to maintenance in favour of quizartinib (Figure 2).

It should be emphasized that a higher number of patients in the quizartinib arm (n=116) entered the maintenance phase compared to the placebo arm (n=92). This suggests that quizartinib may contribute to a condition that allows more patients to reach this phase of treatment. HSCT was part of the treatment policy in the study design in consolidation phase. This means that the study design did not take randomization and stratification into account at this stage of the study, which implies that the groups with and without HSCTs are biased. The QuANTUM-First trial was not designed to explore comparative survival within individual phases of treatment.

Figure 1. KM Plot of OS for Subjects Who Entered the Maintenance Phase With HSCT Prior to Maintenance (ITT Analysis Set)

Abbreviations: HSCT, hematopoietic stem cell transplantation; IRC, Independent Review Committee; ITT, Intent-to-treat.

Figure 2. KM Plot of OS for Subjects Who Entered the Maintenance Phase Without HSCT Prior to Maintenance (ITT Analysis Set)

Abbreviations: HSCT, hematopoietic stem cell transplantation; IRC, Independent Review Committee; ITT, Intent-to-treat.

Table 1. Analysis of OS for Subjects Who Entered Maintenance Phase by HSCT Status (ITT Analysis Set)

Statistics	With HSCT Prior to Maintenance[a]			Without HSCT Prior to Maintenance[b]		
	Quizartinib (N = 70)	Placebo (N = 49)	Analysis (Quizartinib vs. Placebo)	Quizartinib (N = 46)	Placebo (N = 43)	Analysis (Quizartinib vs. Placebo)
Subjects (%) with events (deaths)	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Subjects (%) without events (censored)	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Alive at the time of data cut-off date	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Lost to follow-up	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Withdrawal of consent	[redacted]	[redacted]	—	[redacted]	[redacted]	—
Unstratified Cox regression analysis						
Hazard ratio (relative to placebo)	—	—	1.62	—	—	0.40
95% CI	—	—	0.62, 4.22	—	—	0.19, 0.84
Median OS (months) (95% CI)[c]	[redacted]	[redacted]	—	[redacted]	[redacted]	—
OS rate (%) (95% CI)[d] at:						
12 months	[redacted]	[redacted]	—	[redacted]	[redacted]	—
24 months	[redacted]	[redacted]	—	[redacted]	[redacted]	—
36 months	[redacted]	[redacted]	—	[redacted]	[redacted]	—
48 months	[redacted]	[redacted]	—	[redacted]	[redacted]	—

Abbreviations: CI, confidence interval; HSCT, allogeneic hematopoietic stem cell transplantation; ITT, intent-to-treat; NE, not estimable; OS, overall survival
a Includes subjects who received consolidation chemotherapy + HSCT and those who received HSCT alone during the Consolidation Phase
b Includes subjects who received only consolidation chemotherapy during the Consolidation Phase
c Median OS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.
d Estimated using the Kaplan-Meier method.
Note: OS is the time from Randomization until the date of death from any cause. Denominator for percentages is the number of subjects in the ITT Analysis Set in each HSCT status subgroup.

A3b Response: Demographic and disease baseline characteristics among patients who underwent maintenance therapy with HSCT and without HSCT prior to maintenance are presented in Table 2 and Table 3, respectively.

Table 2. Demographic and disease baseline characteristics prior to maintenance among patients who underwent maintenance therapy with HSCT Prior to maintenance

Characteristic	Quizartinib, N = 70	Placebo, N = 49	Total, N = 119
Analysis Age			
N	xx	xx	xxx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx
Median	xx	xx	xx
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Pooled Age			
<60	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
≥60 - <65	x.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
≥65 - <75	xx.xx (xx.xx%)	x.xx (xx.xx%)	xx.xx (xx.xx%)
Sex			
Female	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Male	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Race			
Asian	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Other	x.xx (x.xx%)	x.xx (xx.xx%)	xx.xx (x.xx%)
White	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Ethnicity			
Hispanic or Latino	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Not collected per local regulations	x.xx (x.xx%)	x.xx (xx.xx%)	xx.xx (x.xx%)
Not Hispanic or Latino	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xxx.xx (xx.xx%)
Height at Baseline (cm)			
N	xx	xx	xxx
Mean	xxx.xx	xxx.xx	xxx.x
SD	x.xx	x.xx	x.xx
Median	xxx.x	xxx	xxx
Minimum	xxx	xxx	xxx
Maximum	xxx	xxx	xxx
Weight at Baseline (kg)	xx	xx	xx
N	xx	xx	xxx
Mean	xx.xx	xx.x	xx.xx
SD	xx.x	xx.xx	xx.xx
Median	xx.xx	xx	xx
Minimum	xx.x	xx	xx

Characteristic	Quizartinib, N = 70	Placebo, N = 49	Total, N = 119
Maximum	xxx	xxx	xxx
Body Surface Area at Baseline (m^2)			
N	xx	xx	xxx
Mean	x.xx	x.x	x.xx
SD	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx
Minimum	x.x	x.xx	x.x
Maximum	x.x	x.xx	x.x
Body Mass Index at Baseline (kg/m^2)			
N	xx	xx	xxx
Mean	xx.xx	xx.xx	xx.xx
SD	x.xx	x.xx	x.xx
Median	xx.xx	xx.x	xx.xx
Minimum	xx.x	xx.xx	xx.x
Maximum	xx.xx	xx.xx	xx.xx
BMI at Baseline (kg/m^2)			
<18.5	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
≥30	xx.xx (xx.xx%)	x.xx (xx.xx%)	xx.xx (xx.xx%)
18.5 - <25	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
25 - <30	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Geographic Region			
Asia/Other Regions	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Europe	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
North America	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
ECOG Performance Status at Baseline			
0 - Fully Active	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
1 - Restricted in Physically Strenuous Activity	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
2 - Ambulatory and Capable of All Selfcare	xx.xx (xx.xx%)	x.xx (xx.xx%)	xx.xx (xx.xx%)
Choice of Anthracycline			
Daunorubicin	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Daunorubicin, Idarubicin	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Idarubicin	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Age at maintenance			
N	xx	xx	xxx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx
Median	xx	xx	xx
Minimum	xx	xx	xx
Maximum	xx	xx	xx
HSCT before maintenance	xx	xx	xx
Yes	xx.xx (xxx.xx%)	xx.xx (xxx.xx%)	xxx.xx (xxx.xx%)
ECOG PS at Maintenance			

Characteristic	Quizartinib, N = 70	Placebo, N = 49	Total, N = 119
0	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
1	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
2	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
3	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Unknown	xx	x	xx

Abbreviations: BMI, body mass index; cm, Centimetre; ECOG, Eastern Cooperative Oncology Group Performance Status; HSCT, hematopoietic stem cell transplantation; kg, kilogram; SD, Standard Deviation.
Source: Daiichi Sankyo DOF, 2024

Table 3. Demographic and disease baseline characteristics prior to maintenance among patients who underwent maintenance therapy without HSCT Prior to maintenance

Characteristic	Quizartinib, N = 46	Placebo, N = 43	Overall, N = 89
Analysis Age			
N	xx	xx	xx
Mean	xx.xx	xx	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx	xx	xx
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Pooled Age			
<60	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
≥60 - <65	xx.xx (xx.xx%)	x.xx (x.xx%)	xx.xx (xx.xx%)
≥65 - <75	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Sex			
Female	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Male	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Race			
American Indian or Alaska native	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Asian	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Black or African American	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Other	x.xx (xx.xx%)	x.xx (x.xx%)	x.xx (xx.xx%)
White	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Ethnicity			
Hispanic or Latino	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Not collected per local regulations	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Not Hispanic or Latino	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Height at Baseline (cm)			
N	xx	xx	xx
Mean	xxx.x	xxx.xx	xxx.xx
SD	x.xx	xx.xx	x.xx
Median	xxx	xxx	xxx

Characteristic	Quizartinib, N = 46	Placebo, N = 43	Overall, N = 89
Minimum	xxx	xxx	xxx
Maximum	xxx	xxx	xxx
Unknown	x	x	x
Weight at Baseline (kg)			
N	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx	xx
Minimum	xx.x	xx.x	xx.x
Maximum	xxx	xxx.x	xxx
Body Surface Area at Baseline (m^2)			
N	xx	xx	xx
Mean	x.x	x.xx	x.x
SD	x.xx	x.xx	x.x
Median	x.x	x.xx	x.x
Minimum	x.x	x.xx	x.xx
Maximum	x.x	x.x	x.x
Body Mass Index at Baseline (kg/m^2)			
N	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	x.xx	x.xx	x.xx
Median	xx.xx	xx.xx	xx.xx
Minimum	xx.xx	xx.xx	xx.xx
Maximum	xx.xx	xx.xx	xx.xx
Unknown	x	x	x
BMI at Baseline (kg/m^2)			
<18.5	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
≥30	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
18.5 - <25	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
25 - <30	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Geographic Region			
Asia/Other Regions	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Europe	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
North America	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
ECOG Performance Status at Baseline			
0 - Fully Active	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
1 - Restricted in Physically Strenuous Activity	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
2 - Ambulatory and Capable of All Selfcare	x.xx (xx.xx%)	x.xx (x.xx%)	x.xx (xx.xx%)
Choice of Anthracycline			
Daunorubicin	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
Idarubicin	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)

Characteristic	Quizartinib, N = 46	Placebo, N = 43	Overall, N = 89
Age at maintenance			
N	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.x
Median	xx.x	xx	xx
Minimum	xx	xx	xx
Maximum	xx	xx	xx
HSCT before maintenance			
No	xx.xx (xxx.xx%)	xx.xx (xxx.xx%)	xx.xx (xxx.xx%)
ECOG PS at Maintenance			
0	xx.xx (xx.xx%)	xx.xx (xx.xx%)	xx.xx (xx.xx%)
1	xx.xx (xx.xx%)	x.xx (xx.xx%)	xx.xx (xx.xx%)
2	x.xx (x.xx%)	x.xx (x.xx%)	x.xx (x.xx%)
Unknown	x	xx	xx

Abbreviations: BMI; body mass index; cm, Centimetre; ECOG, Eastern Cooperative Oncology Group Performance Status; HSCT, hematopoietic stem cell transplantation; kg, kilogram; SD, Standard Deviation.
Source: Daiichi Sankyo DOF, 2024

A3c Response:

Additional subgroup analyses on OS for individuals who entered the maintenance phase with HSCT and without HSCT

a. Propensity Score matched analyses

In addition to the exploratory subgroup analyses in question A3a, a propensity score (PS) matching analyses of the subjects entering the maintenance phase was conducted to help address the nature of the non-randomized population entering the maintenance phase in the QuANTUM-First trial and to account for potential confounding factors between the treatment arms.

Four methods were used for matching: Stratification based on PS, PS matching, Inverse probability treatment weighting (IPTW) and PS for covariate adjustment.

Following covariates were selected to build the PM model. These included those covariates that were unbalanced study baseline or at the initiation of maintenance phase between the treatment arms plus know prognostic factors for acute myeloid leukaemia (AML):

- Age

- Sex
- WBC count at the time of diagnosis of AML
- NPM-1 mutational status at study baseline
- Percentage of bone marrow blasts at study baseline
- Choice of anthracycline
- HSCT prior to the maintenance phase

The PS-based results were similar to unadjusted results (HR [95% CI]: 1.62 [0.62, 4.22]; Table 4). It should be noted that there are only a small number of death events (20 events in total) observed in all subjects who entered the maintenance phase after prior HSCT. As a result, the 95% CI for the HRs of quizartinib versus placebo are very wide, making it challenging to interpret the data and draw definitive conclusions.

The PS-based results in the subgroup of subjects who entered maintenance therapy without HSCT prior to the maintenance phase were also similar to unadjusted results. The HR ratios ranged from 0.4 to 0.46 (Table 4). Again, the number of death events in this analysis is small.

Table 4. HR estimations from PS-based analyses of OS by HSCT status based on unbalanced variables between arms at study baseline or initiation of maintenance (Maintenance Analysis Set)

	With HSCT prior to maintenance phase	Without HSCT prior to maintenance phase
	N = 119	N = 89
Crude (no adjustment)	1.62 (0.62, 4.22)	0.4 (0.19, 0.84)
Stratification	1.83 (0.7, 1.81)	0.46 (0.21, 0.98)
Matching	1.65 (0.63, 4.32)	0.4 (0.16, 0.99)
IPTW	1.67 (0.65, 4.28)	0.41 (0.2, 0.87)
Covariate adjustment	1.61 (0.61, 4.23)	0.43 (0.2, 0.93)

Abbreviations: HR, hazard ratio; HSCT, Hematopoietic Stem Cell Transplantation; IPTW, Inverse Probability of Treatment Weighting; OS, overall survival; PS, Propensity Score.

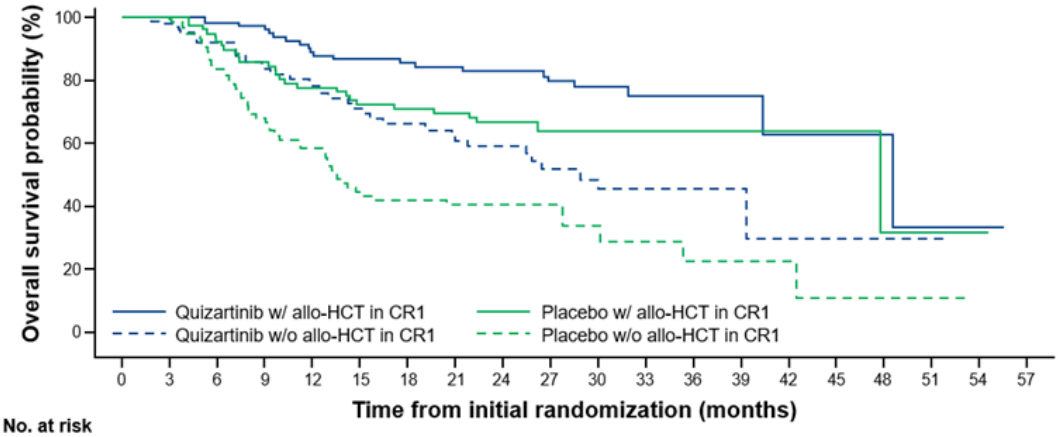
b. Post-hoc analysis for the time-dependent effect of HCST in CR on OS

A post-hoc analysis for the time-dependent effect of HCST in CR on OS, by treatment arm, has been carried out (5).In contract to the propensity score matched analysis of the ITT population, this analysis of patients achieving CR before HSCT showed a OS signal favouring quizartinib.

A Simon-Makuch plot, used to analyse the time-dependent effect of HCST in CR on OS, showed that patients achieving CR on quizartinib had longer OS, regardless of whether they underwent HSCT in first CR (CR1) or not (HR [95% CI]: 0.42 [0.30, 0.60]; Figure 3). The analyses took all three phases of treatment (induction, consolidation, and maintenance) into account. However, the specific benefits in the post-transplant setting, as explored in this analysis, highlight the need for more robust evidence to fully understand its role.

This analysis underscores the potential of quizartinib in improving outcomes for patients post-HSCT. Yet, it also emphasises the challenges in interpreting data with wide confidence intervals and the impact of censoring on long-term outcome analyses. The findings argue for the need for larger, possibly randomised studies to more definitively assess the benefits of quizartinib in this specific patient population.

Figure 3. Post Hoc Analysis[a] for Patients Achieving CR Illustrating the Time-Dependent Effect on OS of HSCT in First CR1 According to Initial Randomization



No. at risk																			
Quizartinib w/allo-HCT in CR1	0	6	63	76	72	72	70	69	67	63	57	50	42	34	29	22	14	3	1
Placebo w/allo-HCT in CR1	0	15	60	60	54	52	51	50	48	43	39	37	32	27	21	20	12	5	3
Quizartinib w/o allo-HCT in CR1[b]	147	138	74	56	50	44	41	37	35	30	25	21	17	15	9	5	3	1	0
Placebo w/o allo-HCT in CR1[b]	150	134	69	53	44	33	31	30	30	25	22	17	14	10	7	4	2	1	0

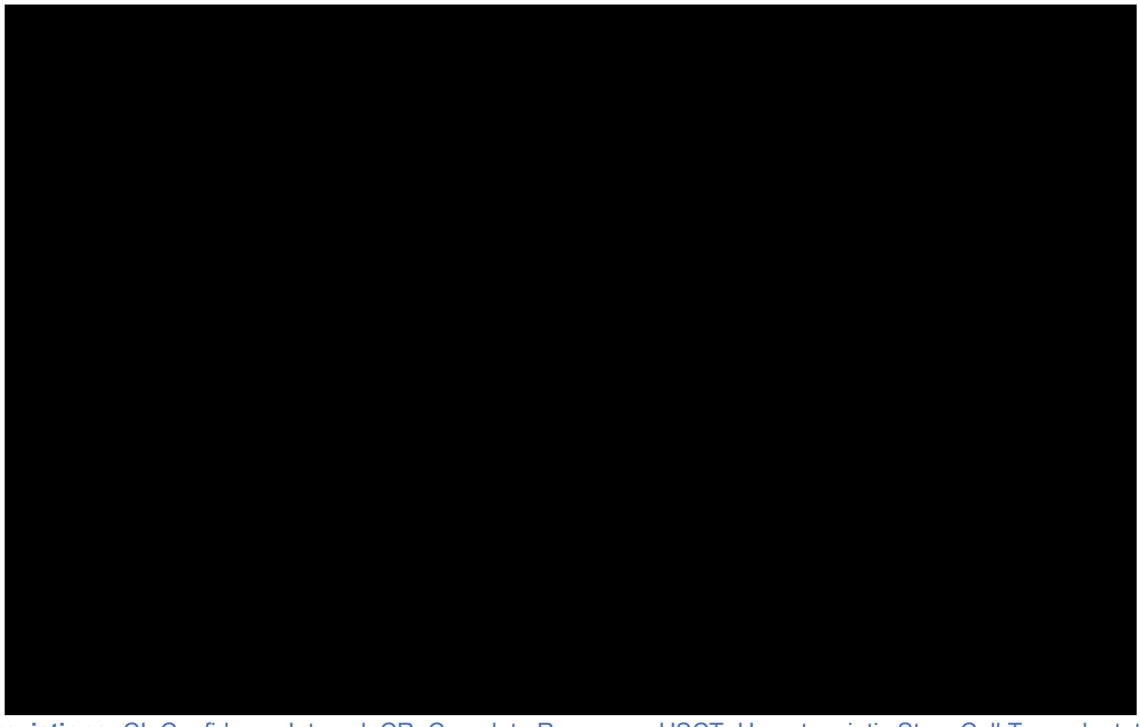
Abbreviations: CR, complete remission; HSCT, allogenic stem cell transplant; OS, overall survival.
Notes: a) Post hoc analysis using the Simon Makuch plot, which takes into account the timing of HSCT occurrence, meaning that once a patient undergoes HSCT, the patient switches from the w/o HSCT category to the w/ HSCT category.
b) W/o HSCT in CR1 refers to CR patients without HSCT in the study or CR patients with HSCT outside CR1. HSCT in CR1 means HSCT after CR1 without evidence of relapse by IRC assessment.

Additional analyses on relapse-free survival (RFS) for individuals who entered the maintenance phase with HSCT and without HSCT

The median RFS (95% CI) was not reached in either treatment arm in the group of subjects with HSCT prior to maintenance (HR [95% CI]: 1.2 [0.47, 3.05]; Table 5). The two KM curves between the two treatment arms in the subjects with HSCT prior to maintenance are overlapping (Figure 4). There are only a small number of events of relapse or death (19 events in total) observed among the two arms, and as a result, the 95% CI for the HR of quizartinib versus placebo is very wide (0.47 to 3.05), thus limiting the interpretation of the results.

In the group of subjects without HSCT prior to maintenance, the median RFS (95% CI) was 39.3 (19.8, NE) months in the quizartinib arm and 27.3 (12.6, NE) months in the placebo arm (HR [95% CI]: 0.63 [0.34, 1.17]; Table 5). There appears to be a clear separation of the two KM curves between the two treatments arms in the subjects without HSCT prior to maintenance in favour of quizartinib (Figure 5).

Figure 4. KM Plot of RFS for Subjects Who Achieved CR in Induction and Entered the Maintenance Phase With HSCT Prior to Maintenance



Abbreviations: CI, Confidence Interval; CR, Complete Response; HSCT, Hematopoietic Stem Cell Transplantation; KM, Kaplan-Meier; NE, non-estimable; RFS, Relapse-Free Survival.

Figure 5. KM Plot of RFS for Subjects Who Achieved CR in Induction and Entered the Maintenance Phase Without HSCT Prior to Maintenance – (ITT Analysis Set)

Abbreviations: CI, confidence interval; CR, complete response; HSCT, haematopoietic stem cell transplantation; KM, Kaplan-Meier; NE, non-estimable; RFS, relapse-free survival.

Table 5. Analysis of RFS for Subjects Who Achieved CR in Induction and Entered the Maintenance Phase by HSCT Status – IRC Assessment (ITT Analysis Set)

Statistics	HSCT Prior to Maintenance[a]			No HSCT Prior to Maintenance[b]		
	Quizartinib (N = 70)	Placebo (N = 49)	Analysis (Quizartinib vs. Placebo)	Quizartinib (N = 46)	Placebo (N = 43)	Analysis (Quizartinib vs. Placebo)
Subjects with CR who entered the Maintenance Phase, n[c]	xx	xx	—	xx	xx	—
Subjects (%) with events	xx (xx.x)	x (xx.x)	—	xx (xx.x)	xx (xx.x)	—
Relapse	x (xx.x)	x (xx.x)	—	xx (xx.x)	xx (xx.x)	—
Death	x (x.x)	x (x.x)	—	x (x.x)	x (xx.x)	—
Subjects (%) without events (censored)	xx (xx.x)	xx (xx.x)	—	xx (xx.x)	xx (xx.x)	—
Unstratified Cox regression analysis						
Hazard ratio (relative to placebo)	—	—	1.20	—	—	0.63
95% CI	—	—	0.47, 3.05	—	—	0.34, 1.17
Median RFS (months) (95% CI)[d]	xx (xx.x, xx)	xx (xx, xx)	—	xx.x (xx.x, xx)	xx.x (xx.x, xx)	—
RFS rate (%) (95% CI)[e] at:						
12 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—
18 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—
24 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—
36 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—
48 months	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	—

Abbreviations: CI, confidence interval; CR, complete response; HSCT, hematopoietic stem cell transplantation; KM, Kaplan-Meier; NE, non-estimable; RFS, relapse-free survival.

Notes: [a] Includes subjects who received consolidation chemotherapy + HSCT and those who received HSCT alone during the Consolidation Phase

[b] Includes subjects who received only consolidation chemotherapy during the Consolidation Phase

[c] Used as denominator for percentage calculation below. Subjects without a documented response of CR are excluded from the analysis.

[d] Median RFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.

[e] Estimated using the Kaplan-Meier method.

[f]. RFS is the time from Randomization, for subjects who achieve CR in the Induction Phase, until the date of documented relapse or death from any cause, whichever comes first.

Similarly, to the OS, a series of PS matching analyses on RFS of the subjects entering the maintenance phase based on the HSCT status (Table 6).

In the group of subjects with HSCT prior to maintenance, the PS-based results in Table 6 were similar to unstratified Cox model results (HR=1.12). Note that there are only a small number of events of relapse or death (19 events in total) observed among the two arms, and as a result, the 95% CIs for the HRs of quizartinib versus placebo are wide, thus limiting the interpretation of the results.

The HR (95% CI) of quizartinib to placebo using an unstratified Cox model was 0.63 (0.34; 1.17) in the group of subjects without HSCT prior to maintenance (Table 6). The PS-based results were similar to unadjusted results. The HRs ranged from 0.54 to 0.66, which is directionally consistent with the unadjusted HR of 0.63.

Table 6. HR estimations from PS-based analyses of RFS by HSCT status based on unbalanced variables between arms at study baseline or initiation of maintenance (Maintenance Analysis Set)

	With HSCT prior to maintenance phase	Without HSCT prior to maintenance phase
	N = 77	N = 89
Crude (no adjustment)	1.2 (0.47, 3.05)	0.63 (0.34, 1.17)
Stratification	1.18 (0.46, 3.03)	0.66 (0.34, 1.26)
Matching	0.74 (0.24, 2.27)	0.54 (0.25, 1.2)
IPTW	1.36 (0.53, 3.55)	0.61 (0.33, 1.14)
Covariate adjustment	1.19 (0.46, 3.06)	0.61 (0.32, 1.18)

Abbreviations: HSCT, hematopoietic stem cell transplantation; IPTW, inverse probability of treatment weighting; RFS, relapse free survival; PS, propensity score.

A4. Priority question: Please provide a table with a breakdown of the number of patients in each trial arm who achieved complete remission (CR) and underwent HSCT, and the number of patients in each treatment group who achieved complete remission with incomplete neutrophil or platelet recovery (CRi) and underwent HSCT. Please specify after what stage of the treatment (i.e. after induction 1, 2 or consolidation) they underwent HSCT.

A4 Response: The breakdown of the number of patients in QuANTUM-First by arm, who achieved CR or CRi and underwent protocol-specific HSCT, and who achieved CR or CRi and underwent all type of HSCT, are presented in Table 76 and Table 87, respectively.

Table 7. Breakdown of the number of patients in QuANTUM-First based on the remission and protocol-specific HSCT status

Remission and protocol-specific HSCT status	Placebo (N = 271)	Quizartinib (N = 268)
CR & Did not received HSCT	xx (xx.xx%)	xx (xx.xx%)
CR & HSCT in consolidation	xx (xx.xx%)	xx (xx.xx%)
CR & HSCT post consolidation	x (x.xx%)	x (x.xx%)
CRi & Did not received HSCT	xx (x.x%)	xx (x.xx%)
CRi & HSCT in consolidation	xx (x.x%)	xx (x.xx%)
CRi & HSCT post consolidation	x (x%)	x (x.xx%)
Did not achieve remission & Did not received HSCT	xx (xx.xx%)	xx (xx.xx%)
Did not achieve remission & HSCT in consolidation	x (x.xx%)	x (x.xx%)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete platelet or neutrophil recovery; HSCT, allogeneic hematopoietic stem cell transplantation.

Table 8. Breakdown of the number of patients in QuANTUM-First based on the remission and all types of HSCT status

CR and HSCT Status – All HSCT	Placebo (N = 271)	Quizartinib (N = 268)
CR & Did not received HSCT	xx (xx.xx%)	xx (xx.xx%)
CR & HSCT post Induction 1	x (x.xx%)	x (x.xx%)
CR & HSCT post Induction 2	x (x.xx%)	x (x.xx%)
CR & HSCT in consolidation	xx (xx.xx%)	xx (xx.xx%)
CR & HSCT post consolidation	xx (x.xx%)	xx (x.xx%)
CRi & Did not received HSCT	xx (x.x%)	xx (x.xx%)
CRi & HSCT post Induction 1	x (x%)	x (x.xx%)
CRi & HSCT post Induction 2	x (x%)	x (x.xx%)
CRi & HSCT in consolidation	xx (x.x%)	xx (x.xx%)
CRi & HSCT post consolidation	x (x%)	x (x.xx%)
Did not achieve remission & HSCT in Induction 1	x (x.xx%)	x (x.xx%)
Did not achieve remission & HSCT in Induction 2	x (x.xx%)	x (x.xx%)
Did not achieve remission & HSCT post Induction 1	xx (x.x%)	x (x.xx%)
Did not achieve remission & HSCT post Induction 2	x (x.xx%)	x (x.xx%)
Did not achieve remission & HSCT in consolidation	x (x.xx%)	x (x.xx%)
Did not achieve remission & HSCT post consolidation	x (x.xx%)	x (x.xx%)
Did not achieve remission & Did not received HSCT	xx (xx.xx%)	xx (xx.xx%)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete platelet or neutrophil recovery; HSCT, allogeneic hematopoietic stem cell transplantation

A5. Priority question: Please provide the HR and 95% CI for CIR in patients with CR during induction (ITT analysis set, CS, Figure 14).

A5 Response: The requested details are included in Table 9 and are in line with Table 29 of the CS.

Table 9. Cumulative incidence of relapse – quizartinib (Adjusted QuANTUM-First population) and midostaurin (RATIFY *FLT3-ITD*+ population)

Method	Comparison	HR (95% CI)
QuANTUM-First unadjusted[a]	Quizartinib vs. placebo	x.xx (x.xx, x.xx)

Abbreviations: CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; HR, hazard ratio; *ITD*, internal tandem duplication.
Source: Daiichi Sankyo, 2023 (6)

A6. Priority question: Please provide assessments of the proportional hazards (PH) assumption (i.e., log cumulative hazard plots and Schoenfeld Residuals tests) for the following outcomes of the QuANTUM-First trial:

a. **OS (primary analysis, ITT analysis set; Company submission [CS], Table 13 and Figure 5)**

b. **CIR in patients with complete remission during induction (Intent-to-treat [ITT] analysis set; CS, Figure 14)**

c. **OS (Censored at the start date of the conditioning regimen for HSCT, ITT analysis set; CS, Table 13 and Figure 6)**

d. **Event-free survival (EFS; primary analysis and sensitivity analyses, ITT analysis set; CS, Table 15)**

e. **Relapse-free survival (RFS) in patients achieving composite complete remission (CRc; ITT analysis set; CS, Table 17 and Figure 10)**

f. **RFS in patients achieving CR (ITT analysis set; CS, Table 18 and Figure 11)**

g. **Duration of CR (ITT analysis set; CS, Table 19 and Figure 12)**

A6a Response: As is shown in Figure 6 and Figure 7, the proportional hazard (PH) assumption appears to be violated in the QuANTUM-First trial primary analysis set for OS.

Figure 6. Log-cumulative hazard curve – QuANTUM-First trial primary analysis set OS

Abbreviations: OS, Overall Survival.

Figure 7. Schoenfeld residual plot – QuANTUM-First trial primary analysis set OS

Abbreviations: OS, Overall Survival.

A6b Response: As is shown in Figure 8 and

Figure 9, the PH assumption is not violated for CIR in patients with CR during induction in the ITT analysis set.

Figure 8. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set CIR in patients with CR during induction

Abbreviations: CIR, cumulative incidence of relapse; CR, complete remission; ITT, intention to treat.

Figure 9. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set CIR in patients with CR during induction

Abbreviations: CIR, cumulative incidence of relapse; CR, complete remission; ITT, intention to treat.

A6c Response: As is shown in Figure 10 and Figure 11, the PH assumption appears to be violated for OS censored at the start date of the conditioning regimen for HSCT in the ITT analysis set.

Figure 10. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set OS censored at the start date of the conditioning regimen for HSCT

Abbreviations: HSCT, allogenic stem cell transplant; ITT, intention to treat; OS, overall survival.

Figure 11. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set OS censored at the start date of the conditioning regimen for HSCT

Abbreviations: HSCT, allogenic stem cell transplant; ITT, intention to treat; OS, overall survival.

A6d Response: As is shown in Figure 12 and

Figure 13, the PH assumption appears to be violated for EFS in the ITT analysis set. This is also true for the EFS sensitivity analysis shown in Figure 14 and Figure 15 for sensitivity analysis 1 and Figure 16 and Figure 17 for sensitivity analysis 2 and Figure 18 and Figure 19 for sensitivity analysis 3.

Figure 12. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set EFS

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 13. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set EFS

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 14. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set EFS sensitivity analysis 1

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 15. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set EFS sensitivity analysis 1

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 16. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set EFS sensitivity analysis 2

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 17. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set EFS sensitivity analysis 2

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 18. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set EFS sensitivity analysis 3

Abbreviations: EFS, event free survival; ITT, intention to treat.

Figure 19. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set EFS sensitivity analysis 3

Abbreviations: EFS, event free survival; ITT, intention to treat.

A6e Response: As is shown in Figure 20 and Figure 21 , the PH assumption appears to be violated RFS in patients achieving composite remission in the ITT analysis set.

Figure 20. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set RFS in patients achieving CRc

Abbreviations: CRc, composite complete remission; ITT, intention to treat; RFS, relapse free survival.

Figure 21. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set RFS in patients achieving CRc

Abbreviations: CRc, composite complete remission; ITT, intention to treat; RFS, relapse free survival.

A6f Response: As is shown in Figure 22 and Figure 23, the PH assumption appears to be violated for RFS in patients achieving CR in the ITT analysis set.

Figure 22. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set RFS in patients achieving CR

Abbreviations: CR, complete remission; ITT, intention to treat; RFS, relapse free survival.

Figure 23. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set RFS in patients achieving CR

Abbreviations: CR, complete remission; ITT, intention to treat; RFS, relapse free survival.

A6g Response: As is shown in Figure 24 and Figure 25, the PH assumption appears to be violated for duration of CR in the ITT analysis set.

Figure 24. Log-cumulative hazard curve – QuANTUM-First trial ITT analysis set duration of CR

Abbreviations: CR, complete remission; ITT, intention to treat.

Figure 25. Schoenfeld residual plot – QuANTUM-First trial ITT analysis set duration of CR

Abbreviations: CR, complete remission; ITT, intention to treat.

A7. Document B, Table 20 indicates that a subset of individuals may have received 'intervening AML therapy' other than conditioning regimens between protocol treatment and HSCT. Please provide details and the number of patients in each treatment group receiving intervening therapies.

A7 Response: xx subjects in the quizartinib and xx in the placebo group had a non-protocol specified HSCT, and xx (xx%) and xx (xx%) of the subjects respectively in the two groups had non-protocol specified AML drug therapy between end of last protocol treatment in maintenance phase until date of non-protocol specified HSCT (4). Most common agent was cytarabine in xx (xx%) and xx (xxx%) subjects in the quizartinib and placebo group respectively. A detailed table is presented in Table 10.

Table 10. Intervening AML therapy for patients with non-protocol specified HSCT (ITT Analysis Set)

	Quizartinib (N=268)	Placebo (N=271)
Subjects with non-protocol specified HSCT	xx	xx
Subjects with any non-protocol specified AML drug therapy	xx	xx
Antineoplastic Agents	xx	xx
Cytarabine	xx (xx.x)	xx (xxx)
Fludarabine	x (xx.x)	x (xx.x)
Fludarabine Phosphate	x (xx.x)	x
Busulfan	x (xx.x)	x (xx.x)
Gilteritinib	x (xx.x)	x
Idarubicin	x (xx.x)	x (xx.x)
Idarubicin Hydrochloride	x (xx.x)	x
Mitoxantrone	x (xx.x)	x (xx.x)
Thiotepa	x (xx.x)	x
Amsacrine	x (x.x)	x (xx.x)
Combinations Of Antineoplastic Agents	x (x.x)	x
Cyclophosphamide Monohydrate	x (x.x)	x
Daunorubicin	x (x.x)	x
Enocitabine	x (x.x)	x
Etoposide	x (x.x)	x (xx.x)
Gemtuzumab Ozogamicin	x (x.x)	x (xx.x)
Gilteritinib Fumarate	x (x.x)	x
Melphalan	x (x.x)	x (xx.x)
Mercaptopurine	x (x.x)	x
Mitoxantrone Hydrochloride	x (x.x)	x (xx.x)
Sorafenib	x (x.x)	x (xx.x)
Azacitidine	x	x (xx.x)
Midostaurin	x	x (xx.x)
Immunosuppresants	x	x
Antithymocyte Immunoglobulin (Rabbit)	x (xx.x)	x

Abbreviations: AML, acute myeloid leukaemia; HSCT, allogenic stem cell transplant; N: number of subjects in analysis set (Denominator for percentages calculation is the number of patients with AML therapy)

A8. In the post-hoc analyses (Section B.2.6.4), of 157 patients with CRc treated with quizartinib after induction, 66 (42%) had minimal residual disease (MRD) negativity versus 58 (38%) among the 151 patients with CRc treated with placebo as assessed at the time of CR or CRi. Please comment on the role of MRD assessment in the QuANTUM-First trial with respect to treatment choices including HSCT uptake.

A8 Response: FLT3-ITD MRD was a biomarker endpoint assessed in a post-hoc analysis (7). The MRD results were not available during the trial and therefore could not be used in the decision of treatment choices including HSCT uptake.

Sorafenib

A9. Priority Question: Sorafenib maintenance therapy is a recommended by the NHS as a maintenance treatment option for adults with *FLT3-ITD*+ AML post HSCT. Clinical advice to the EAG indicated that it is now widely used in this population.

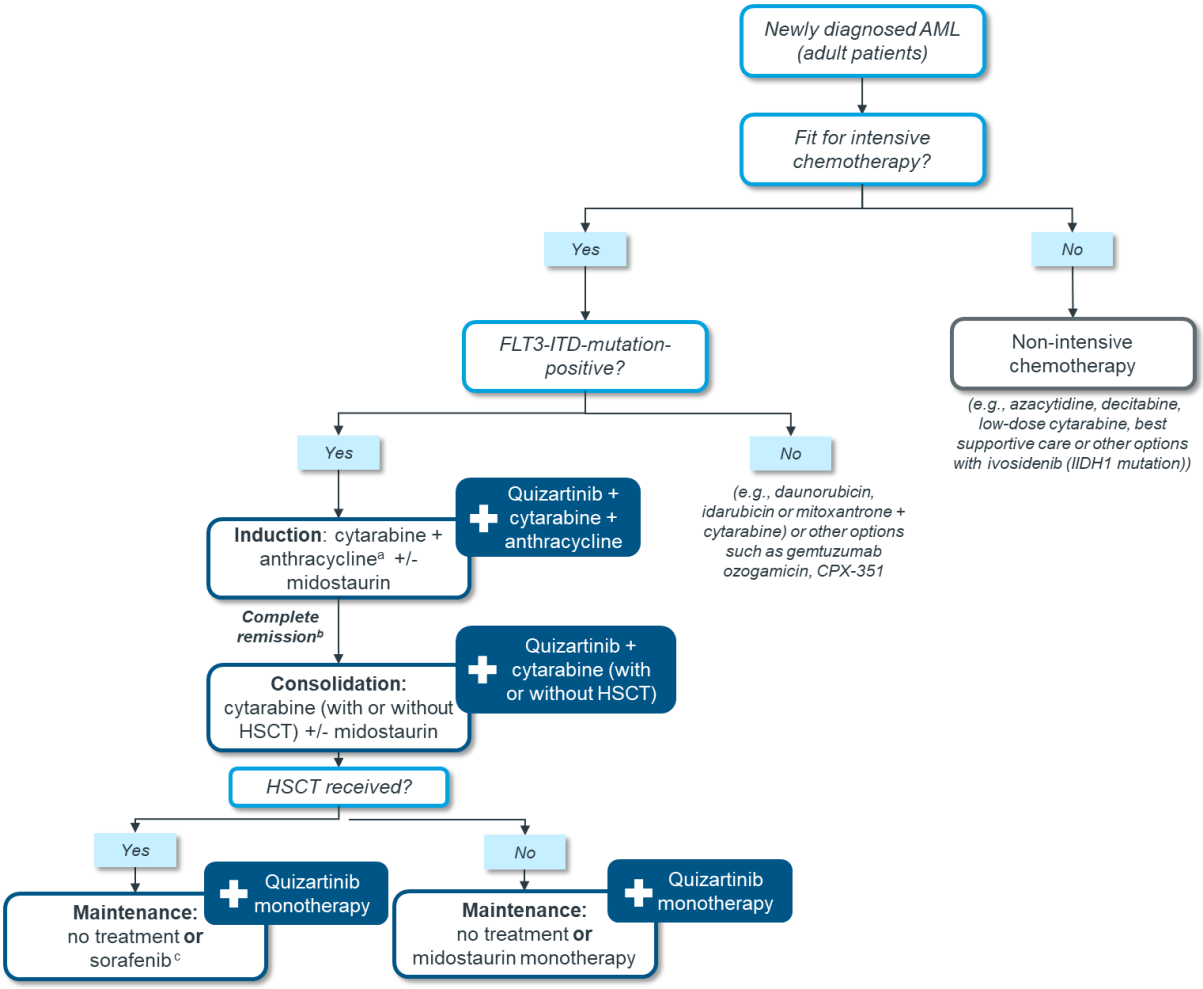
a. **Please add sorafenib to Figure 3 of the CS (Current Treatment Pathway).**

b. **Please present and discuss evidence comparing the effectiveness and safety of these two therapies in this population.**

c. **Please provide an indirect treatment comparison of quizartinib with sorafenib maintenance therapy for adults with *FLT3-ITD*+ AML post HSCT.**

A9a Response: The updated current treatment pathway is provided in Figure 26.

Figure 26. Proposed positioning of quizartinib within current treatment pathway



Abbreviations: AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase 3; HSCT, haematopoietic stem cell transplant; ITD, internal tandem duplication.
References: RM Partners, 2020 (8); ELN, 2022 (9); NHS England, 2023 (10).
Notes: a. In the NHS Pan London guidelines daunorubicin is recommended whereas in the ELN guidelines either daunorubicin or idarubicin are recommended b. complete remission or complete remission with incomplete haematologic recovery. c. sorafenib is not licenced in this indication, however, has been included on the basis of an NHS England clinical commissioning policy

A9b&c Response: A top-line feasibility assessment of an indirect treatment comparison (ITC) of quizartinib vs sorafenib using CIR and OS data from the QuANTUM-First trial and several sorafenib trials post HSCT was conducted focussing on trial differences and the quality of evidence that can be generated from an ITC. The alignment of inclusion and exclusion criteria between the trials was assessed to identify differences between the trials and understand if individual patient-level data (IPD) of QuANTUM-First can be modified to match that of the sorafenib trials. Baseline characteristics were compared to assess if there is enough heterogeneity to support the rationale for conducting a matching-adjusted indirect treatment comparison (MAIC), and a sufficient number of parameters available for matching, making it

technically feasible to conduct the MAIC. Differences were reviewed for outcomes measured, length of study, and follow-up periods, which would influence the comparability of study outcomes. Heterogeneity in study design and conduct were noted to identify bias introduced by differences across the trials that cannot be adjusted for. Two sorafenib studies were assessed SORMAIN and Xuan/Xu (11, 12), in line with the 2023 National Health Service (NHS) evidence review of sorafenib maintenance for FLT3-ITD AML undergoing HSCT (13).

Differences in the inclusion criteria between QuANTUM-First and Xuan/Xu were the age restrictions used, which were more narrow in Xuan/Xu than in QuANTUM-First (18-60 years versus 18-75 years). Meaningful differences in study design included the dosing of sorafenib in Xuan/Xu which was 400mg orally twice daily whereas in the United Kingdom (UK), standard dosing would start with 400mg daily and increase to 400mg orally twice daily after 6 weeks. Additionally, Xuan/Xu allowed for patients to be treated with sorafenib before transplantation, which is not in line with NHS guidelines where sorafenib is only used after transplant. Another important trial characteristic in Xuan/Xu was the open-label design, wherein patients either received open-label sorafenib treatment or no maintenance treatment. The Xuan/Xu study was conducted exclusively in China, raising questions about the transferability of results from the Chinese setting to the UK, considering potential influences of race on AML treatment response, as well as in terms of differences in local treatment practices. Finally, patients needed to be in CR before and after HSCT, which differed from QuANTUM-First where patients with and without CR were eligible for HSCT was well as maintenance treatment. The trial reported OS and CIR outcomes suitable for analysis.

A relevant difference in the inclusion criteria between QuANTUM-First and SORMAIN was the restriction in SORMAIN to patients who achieved CR post-HCT in order to receive sorafenib maintenance treatment, which was not imposed in QuANTUM-First. A meaningful limitation of the SORMAIN trial was the sample size of 88 patients, which represented 44% of the targeted sample size of the trial according to the power calculations. Due to difficulties in recruitment, patient recruiting was discontinued prior to inclusion of a sufficient sample size. The trial was therefore underpowered. The trial reported OS outcomes suitable for analysis.

The company intends to conduct an ITC to provide comparative evidence for quizartinib versus sorafenib, to be supplied by Friday 17th May 2024, however this remains contingent on finalizing the assessment of feasibility,

Indirect treatment comparisons

A10. Priority question: Please assess the PH assumption for the following outcome data used within the indirect treatment comparisons (CS, Section B.2.8 and Appendix M):

a. **RATIFY trial *FLT3-ITD* population data (Rücker et al, ref. 84 of the CS) for OS**

A10a Response: As is shown in Figure 27 and Figure 28, the PH assumption appears to be violated for the RATIFY trial *FLT3-ITD* population data for OS.

Figure 27. Log-cumulative hazard curve – RATIFY trial *FLT3-ITD* population data for OS

Abbreviations: FLT3-ITD, FMS like Tyrosine Kinase 3 internal tandem duplication; OS, overall survival.

Figure 28. Schoenfeld residual plot - RATIFY trial *FLT3-ITD* population data for OS

Abbreviations: FLT3-ITD, FMS like Tyrosine Kinase 3 internal tandem duplication; OS, overall survival.

b. RATIFY trial *FLT3-ITD* population data (Rücker et al, ref. 84 of the CS) for CIR

A10b Response: As is shown in Figure 29 and Figure 30, the PH assumption appears to be violated for the RATIFY trial *FLT3-ITD* population data for CIR.

Figure 29. Log-cumulative hazard curve - RATIFY trial FLT3-ITD population data for CIR

Abbreviations: CIR, cumulative incidence of relapse; FLT3-ITD, FMS like Tyrosine Kinase 3 internal tandem duplication.

Figure 30. Schoenfeld residual plot - RATIFY trial *FLT3-ITD* population data for CIR

Abbreviations: CIR, cumulative incidence of relapse; FLT3-ITD, FMS like Tyrosine Kinase 3 internal tandem duplication.

A11. Priority question: Please clarify the assessments made within the 'Cox proportional hazards test' (CS, Appendix M, p25) and specifically how PH has been assessed within the analyses of CIR which assume competing risks of relapse and death.

A11 Response: PH testing has been done in three ways for OS and CIR. For the whole QuANTUM-First ITT population; the QuANTUM-First ITT population under 60 years of age; and the QuANTUM-First ITT population under 60 years of age weighted to match RATIFY ITD population based on Rucker et al. For testing PH for CIR, all competing events (deaths) were considered as censored at time of death.

As is shown in Figure 31 and Figure 32, the PH assumption appears to be violated for OS for the QuANTUM-First ITT population under 60 year of age.

Figure 31. Log-cumulative hazard curve - PH Testing for QuANTUM-First ITT population under 60 years of age for OS

Abbreviations: ITT, intention to treat; OS, overall survival; PH, proportional hazard.

Figure 32. Schoenfeld residual plot - PH Testing for QuANTUM-First ITT population under 60 years of age for OS

Abbreviations: ITT, intention to treat; OS, overall survival; PH, proportional hazard.

As is shown in Figure 33 and Figure 34, the PH assumption appears to be violated for OS for the QuANTUM-First ITT population under 60 year of age weighted to match the RATIFY ITD population.

Figure 33. Log-cumulative hazard curve - PH Testing for QuANTUM-First ITT population under 60 years of age weighted to match RATIFY ITD for OS

Abbreviations: ITD, internal tandem duplication; ITT, intention to treat; OS, overall survival; PH, proportional hazard.

Figure 34. Schoenfeld residual plot - PH Testing for QuANTUM-First ITT population under 60 years of age weighted to match RATIFY ITD for OS

Abbreviations: ITD, internal tandem duplication; ITT, intention to treat; OS, overall survival; PH, proportional hazard.

As is shown in Figure 35 and Figure 36, the PH assumption appears to be held for CIR for the QuANTUM-First ITT population under 60 year of age.

Figure 35. Log-cumulative hazard curve - PH Testing for QuANTUM-First ITT population under 60 years of age for CIR

Abbreviations: CIR, cumulative incidence of relapse; ITT, intention to treat; PH, proportional hazard.

Figure 36. Schoenfeld residual plot - PH Testing for QuANTUM-First ITT population under 60 years of age for CIR

Abbreviations: CIR, cumulative incidence of relapse; ITT, intention to treat; PH, proportional hazard.

As is shown in Figure 37 and Figure 38, the PH assumption appears to be held for CIR for the QuANTUM-First ITT population under 60 year of age weighted to match the RATIFY ITD population.

Figure 37. Log-cumulative hazard curve - PH Testing for QuANTUM-First ITT population under 60 years of age weighted to match RATIFY ITD for CIR

Abbreviations: CIR, cumulative incidence of relapse; ITD, internal tandem duplication; ITT, intention to treat; PH, proportional hazard.

Figure 38. Schoenfeld residual plot - PH Testing for QuANTUM-First ITT population under 60 years of age weighted to match RATIFY ITD for CIR

Abbreviations: CIR, cumulative incidence of relapse; ITD, internal tandem duplication; ITT, intention to treat; PH, proportional hazard.

A12. Priority question: Please justify that the treatment effect modifiers identified for OS (CS, Section B.2.8.3) and used within the Indirect Treatment Comparisons (CS, Section B.2.8 and Appendix M) are also treatment effect modifiers for CR and CIR.

A12 Response: For the ITC, treatment effect modifiers (TEMs) were identified following National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 18 (14), which indicates that evidence should be provided showing that all parameters adjusted for are TEMs or that the degree of imbalance between the trials is sufficient enough to make a material difference. TSD 18 also references the NICE Method Guidance, wherein it is stated that each variable selected should be supported by systematic review, external quantitative evidence or expert opinion.

The NICE Method Guidance was followed for the OS outcome as reporting of TEMs across clinical subgroups was more readily available for this outcome in available publications for RATIFY. From this, coupled with an interaction analysis and the opinion of three experts, the list of TEMs for OS was decided. However, the potential

TEMs for CR and CIR could not be evaluated via the same procedure as the TEMs for OS as the available literature did not report on these outcomes. To overcome this, clinicians were consulted as to the applicability of the OS TEMs to the CR and CIR outcomes of interest. It was during this consultation that the OS TEMs were confirmed to be applicable as TEMs for CR and CIR. It is also important to note that the number of overlapping parameters for consideration as TEMs was low between the QuANTUM-First and RATIFY populations, so there was limited scope to expand on the TEMs considered by outcome.

A13. Priority question: Please explain why the matching adjustment via propensity score weighting has greatly impacted on the CIR in the placebo arm of the QuANTUM-First trial, but not on the Quizartinib arm (CS, Figure 18).

A13 Response: During the matching adjustment procedure, there were several patients in both treatment arms with high weights owing to high platelet counts, which were under-represented in the QuANTUM-First trial population.

The higher impact of matching in the placebo arm is explained by the fact that a higher proportion of these patients (with high weights) experienced relapse in the placebo arm, compared with quizartinib.

A14. Priority question: Please explain how Age and Platelet Count are included within the multilevel network meta-regression (ML-NMR) analyses as continuous variables when the standard deviation for these variables is not reported in the RATIFY *FLT3-ITD*+ population (CS, Appendix M, Table 1, Table 3 and Table 6).

A14 Response: Where the standard deviations for age and platelet count were not reported in the RATIFY FLT3-ITD+ population, an assumption was made based on the range rule (15), which says that the range of the observed data (minimum to maximum) is roughly equal to four times the standard deviation. Given that the minimum and maximum values for both age and platelet count were available, the standard deviation for the purposes of the ML-NMR was assumed to be (maximum – minimum) / 4.

A15. Priority question: Please provide statistical code for all ML-NMR analyses presented in CS, Appendix M

A15 Response: The statistical code for all ML-NMR analyses is provided in the Appendix 1. Supporting question A15.

A16. Priority question: Please provide estimates (mean, standard deviation, and 2.5% and 97.5% creditable intervals) for the Quizartinib vs Midostaurin indirect comparisons from the ML-NMR models for CR, CIR and OS (CS, Appendix M, Table 2, Table 5 and Table 7 respectively).

A16 Response: The indirect estimates for CR, CIR and OS quizartinib versus midostaurin were provided in Table 11, Table 12, and Table 13, respectively.

However, although population-adjusted values are requested, the efficacy estimates are similar in both populations due to the shared effect modifier assumption. The calculated effect size, in terms of HRs or ORs, is similar to a simple Bucher ITC. This is because the coefficients for the treatment effect, when interacted with treatment effect modifiers, would cancel out of the equation when calculating the indirect treatment effects for quizartinib versus midostaurin. The shared effect modifier assumption is clarified below, and the paper by Philippo et al., 2023 (16) is referenced for further details.

In the fitted ML-NMR model, the underlying assumption is that of shared effect modification (SEM). This implies that each effect modifier alters the relative treatment effect (RTE) identically across all treatments. This assumption is attributable to the available data. Specifically, the data requirements for estimating a treatment effect and independent effect modifier interaction terms for a given treatment *k* are either*:*

a) IPD from one or more trials including treatment *k*, or

b) A sufficient quantity of aggregate data studies including treatment *k*, with enough variation in covariate values (equivalent to the requirements for a standard aggregate data meta-regression) (17).

Although an ML-NMR can, in principle, accommodate non-SEM data, the aforementioned requirements are rarely met in the HTA setting. Therefore, SEM is assumed for the same class. This is the case in the current network, as there is one trial with available IPD, and one aggregate study with treatment *k*. Hence, the available

data was insufficient to enable the calculation of independent treatment interaction effects.

Table 11. CR OR estimates - ML-NMR Fixed effects models

	QuANTUM—First ITD+				QuANTUM—First ITD+ <60 years			
Comparison	**Mean**	**SD**	**2.5% CrI**	**97.5% CrI**	**Mean**	**SD**	**2.5% CrI**	**97.5% CrI**
In a QuANTUM-First like population								
Quizartinib vs midostaurin	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
In a QuANTUM-First < 60 years like population								
Quizartinib vs midostaurin	NA	NA	NA	NA	x.xx	x.xx	x.xx	x.xx
In a RATIFY like population								
Quizartinib vs midostaurin	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

Abbreviations: CrI, Credible interval; ML-NMR, Multi-level network meta-regression; NA, not applicable; SD, Standard deviation.

Table 12. CIR Population-average conditional HR estimates - ML-NMR Fixed effects M-Spline models

	QuANTUM—First ITD+				QuANTUM—First ITD+ <60 years			
Comparison	**Mean**	**SD**	**2.5% CrI**	**97.5% CrI**	**Mean**	**SD**	**2.5% CrI**	**97.5% CrI**
In a QuANTUM-First like population								
Quizartinib vs midostaurin	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
In a QuANTUM-First < 60 years like population								
Quizartinib vs midostaurin	NA	NA	NA	NA	x.xx	x.xx	x.xx	x.xx
In a RATIFY like population								
Quizartinib vs midostaurin	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

Abbreviations: CrI, Credible interval; ML-NMR, Multi-level network meta-regression; NA, not applicable; SD, Standard deviation.

Table 13. OS Population-average conditional HR estimates - ML-NMR Fixed effects M-Spline models

	QuANTUM—First ITD+				QuANTUM—First ITD+ <60 years			
Comparison	**Mean**	**SD**	**2.5% CrI**	**97.5% CrI**	**Mean**	**SD**	**2.5% CrI**	**97.5% CrI**
In a QuANTUM-First like population								
Quizartinib vs midostaurin	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
In a QuANTUM-First < 60 years like population								
Quizartinib vs midostaurin	NA	NA	NA	NA	x.xx	x.xx	x.xx	x.xx
In a RATIFY like population								
Quizartinib vs midostaurin	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

Abbreviations: CrI, Credible interval; ML-NMR, Multi-level network meta-regression; NA, not applicable; SD, Standard deviation.

A17. Priority question: The *FLT3-ITD*+ subgroup in RATIFY excludes participants over 60 years, lacks CRc outcomes data and several relevant treatment effect modifiers. To address these limitations, and as additional supportive evidence, please conduct an unanchored matching adjusted indirect comparison of Quizartinib vs Midostaurin using OS, CRc and CIR data from the Quizartinib arm of the QuANTUM-First trial and the Midostaurin arm of the AMLSG 16-10 trial.(18)

A17 Response: A top-line feasibility assessment of an ITC of quizartinib versus midostaurin, utilising OS, CRc and CIR data from the quizartinib arm of the QuANTUM-First trial and the midostaurin arm of the AMLSG 16-10 trial, was conducted. This assessment focused on differences between the trials and the quality of evidence that can be generated from an ITC.

The alignment of inclusion and exclusion criteria between the trials was evaluated to understand if IPD of QuANTUM-First can be modified to match that of AMLSG 16-10. Baseline characteristics were compared to assess if there is sufficient heterogeneity between trials to support the rationale for conducting the MAIC, and whether there are enough parameters available for matching, thereby making it technically feasible to conduct the MAIC. Differences in measured outcomes, length of study, and follow-up periods were reviewed, as these factors would influence the comparability of study outcomes. Heterogeneity in study design and conduct was also reviewed to identify any bias introduced by differences across the trials that cannot be adjusted for.

Differences in the inclusion criteria between QuANTUM-First and AMLSG 16-10 are presented in Table 1413. The comparison of inclusion and exclusion criteria revealed heterogeneity between the QuANTUM-First and AMLSG 16-10 populations. The eligible population of QuANTUM-First was somewhat older as it included patients aged 18 to 75 years old, whereas the AMLSG 16-10 population consisted of patients aged 18 to 70 years old. The study designs differed, with QuANTUM-First being a double-blinded randomised controlled trial, and AMLSG 16-10 being a single-arm open-label trial. Outcome definitions were not reported for the AMLSG 16-10 trial but were assumed to be comparable, given that QuANTUM-First used standardised and widely used outcome definitions.

Table 14. Eligibility criteria of QuANTUM-First and AMLSG 16-10

Trial	QuANTUM-First	AMLSG 16-10
Eligible patient population	Patients 18 to 75 years of age, who had newly diagnosed FLT3-ITD (+) AML	Patients 18 to 70 years of age, who had newly diagnosed FLT3-ITD (+) AML, including de novo AML, secondary AML following an antecedent myeloid neoplasm, and therapy-related AML
Investigated treatments[a]	**Induction:** Quizartinib + Standard induction chemotherapy (cytarabine + daunorubicin or Idarubicin) **Consolidation:** Quizartinib + Standard consolidation chemotherapy (high dose cytarabine) chemotherapy **Maintenance:** Quizartinib *Note: Transplantation (Allogeneic HSCT) is one of the options for consolidation therapy, either alone or following consolidation treatment with cytarabine and quizartinib/placebo (see CS Section B.2.3, Table 5)*	**Induction:** Midostaurin + Standard induction chemo (cytarabine + daunorubicin) **Consolidation:** Midostaurin + Standard consolidation chemotherapy (high dose cytarabine) **Maintenance:** Midostaurin as 1-year maintenance therapy *Note: all patients were intended to receive hematopoietic-cell transplant (HSCT).*
Comparators	**Induction:** Placebo + Standard induction chemo (cytarabine + Anthracycline [Daunorubicin or Idarubicin]) **Consolidation:** Placebo + Standard consolidation chemotherapy (high dose cytarabine) **Maintenance:** Placebo	NA
Primary outcome	OS	EFS
Secondary outcomes	EFS, CRc and CR after induction, CRc and CR with FLT3-ITD MRD negativity following induction therapy. *Note: Several EFS definitions were considered in the statistical analyses*	CR rate, RFS, OS, CIR, cumulative incidence of death in CR, FLT3 plasma inhibitory activity, allogeneic HSCT
Exploratory endpoints	RFS, Duration of CR, CRc and CR at the end of the first Induction cycle, CRh, MLFS rate, RFS in subjects who enter the Maintenance Phase, Transplantation rate, QoL, HCRU	
Trial design		
Randomisation	1:1, stratified by age, region, and white blood cell count	Single-arm, open label
Blinding	Double-blinded	
Median follow-up time	39 months	40 months
Sample size	539	440
Prior and Concomitant therapy[b]	No prior or concomitant therapy, with exceptions	No prior or concomitant therapy, with exceptions

Abbreviations: FLT3-ITD (+) AML, FLT3-internal-tandem-duplication-positive Acute Myeloid Leukaemia CR, Complete Remission; CRc, Composite Complete Remission; CRh, CR with partial hematologic recovery; DFS, disease-free survival; EFS, Event-Free Survival; FLT3 = FMS-Like Tyrosine Kinase 3; HCRU healthcare resource use; HCST, hematopoietic cell transplantation; ITD, internal tandem duplication; MLFS, morphologic leukaemia-free state; MRD, minimal residual disease, OS, Overall Survival; QoL, quality-of-life; RFS, relapse-free survival

Notes: a Consolidation therapy with cytarabine was the same for individuals <60 years in both trials. After the first induction chemotherapy cycle, patients with residual disease may receive a second cycle of chemotherapy with either 7 + 3 or 5 + 2 regimens plus quizartinib or placebo in QuANTUM-First, according to institutional standard practice.

Differences in baseline characteristics of the QuANTUM-First and the AMLSG 16-10 populations were assessed and presented in Table 1514. The AMLSG 16-10 reported a higher proportion of younger patients, more female patients, patients with a higher allelic ratio, and patients with higher platelet counts but lower haemoglobin counts, compared to the patients in the QuANTUM-First trial. Both bone marrow blasts and NPM1 mutations were slightly more prevalent in the AMLSG 16-10 trial population. Due to reporting limitations in both trials, other characteristics could not be assessed for similarity across the studies.

Table 15. Baseline characteristics of QuANTUM-First and AMLSG 16-10

	QuANTUM-First		AMLSG 16-10
	Quizartinib (N = 268)	**Placebo (N = 271)**	**Midostaurin (N=440)**
Median age (range), years	56.0 (23,75)	56.0 (20, 75)	54.1 (18,70)
Gender, Female, n (%)	144 (53.7)	150 (55.4)	249 (59)
ECOG			
0	87 (32)	98 (36)	169 (38)
1	134 (50)	136 (50)	218 (50)
2	47 (18)	36 (13)	53 (12)
Haemoglobin, median (range)	42.5 (80, 750)	11.3 (48, 123)	9.0 (4.1,18.1)
Platelets, Median (10^9/L)	22 (3, 136)	23 (3, 387)	59 (5,681)
Subtype of FLT3 mutation with an allelic ratio cut-off of 0.5, n (%)			
TKD	0 (0)	0 (0)	16 (4)
ITD with a low ratio (≤0.5)	135 (50.4)	143 (52.8)	196 (45)
ITD with a high ratio (>0.5)	132 (49.3)	128 (47.2)	242 (55)
Cytogenetic risk			
Favourable	14 (5.2)	19 (7.0)	0 (0)
Intermediate	197 (73.5)	193 (71.2)	386 (88)
Adverse	19 (7.1)	27 (10.0)	26 (6)
Unknown	38 (14.2)	31 (11.4)	28 (6)
Absolute neutrophil count per mm^3, median (range)	0.1 (0, 19.3)	0.1 (0, 17.0)	-
White blood cell count (10^3/µL)			
<40 × 10^9/L	135 (50.4)	137 (50.6)	-
≥40 × 10^9/L	133 (49.6)	134 (49.4)	-
Median (10^9/L)	NA	NA	41.8 (0.3,420)
Bone marrow blasts, median (range)	72 (0, 98.6)	75 (0, 98)	80 (0,100)
NPM1 mutation, n (%)	142 (53.0)	140 (51.7)	266 (60)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; NPM1, nucleophosmin gene; TKD, tyrosine kinase domain

In summary, the top-line feasibility assessment indicated that a MAIC of quizartinib versus midostaurin is likely technically possible using the QuANTUM-First and AMLSG 16-10 trials. However, significant limitations arise from the restricted evidence base, namely the single-arm nature of AMLSG 16-10, resulting need to conduct an unanchored MAIC against QuANTUM-First. For a MAIC to be conducted, baseline characteristics reported for the trials should include all relevant treatment effect

modifiers (TEMs) (i.e. platelet count, sex, age. NPM1, allelic ratio, bone marrow blasts, cytogenic risk, white blood cell (WBC) count, absolute neutrophil count (ANC), geographic region, race) to allow for a fair assessment of the relative treatment effect in the matched population. While some parameters can be matched for, the comprehensiveness of these can be questioned. Additionally, as no common comparator is available and only an unanchored MAIC is feasible, additional emphasis should be put on the availability of all relevant prognostic factors in addition to TEMs. These factors need to be matched such that the absolute treatment effect of the matched population is aligned with the target population. Given the limited availability of prognostic factors, an unanchored MAIC of QuANTUM-First and AMLSG 16-10 is expected to fall short of full alignment of the patient population, and results are expected to be affected by bias.

Overall, it is not expected that conducting an ITC using evidence from QuANTUM-First and AMLSG 16-10 will generate evidence that is more reliable or robust than the existing MAIC and ML-NMR of QuANTUM-First and RATIFY or add considerable value to the existing analyses.

A18. Please clarify what the ORs reported in CS, Appendix M, Table 1 and Table 3 are measuring.

A18 Response: The odds ratios (ORs) reported in Table 1 of the CS, Appendix M, are the calculated odds of complete remission calculated based on published summary statistics from the Rücker et al. publication (19) on ITD+ patients in the RATIFY trial or IPD from QuANTUM-First. It was noted that the ORs reported in the final row of Table 3 in the company submission (CS) Appendix M were duplicated from Table 1 in CS Appendix M and should not have been included in this table. Please see below (Table 16) a revised version of CS, Appendix M, Table 3.

Table 16. (Revised CS, Appendix M, Table 3) CIR and baseline characteristics employed in ML-NMR

Baseline characteristic	QuANTUM-First ITD	QuANTUM-First ITD <60 years	RATIFY ITD+ population
Age, mean	54.0	xx.x	47.1
Age, sd	12.6	x.x	NR
Sex, male, %	41	xx	45
Platelet count, x 10^9/l, mean	29.8	xx.x	44.6
Platelet count, x 10^9/l, sd	23.1	xx.x	NR
NPM1 mutation status, positive, %	68	xx	57

Abbreviations: CR, complete remission; CrI, credible interval; ITD, internal tandem duplication; ML-NMR, multi-level network meta regression; *NPM1*, nucleophosmin 1; NR, not reported; OR, odds ratio.
References: Rucker et al. (20); Daiichi Sankyo, 2022 (21)

Safety and health-related quality of life

A19. Priority question: Document B does not discuss the relative safety and impact on health-related quality of life between quizartinib and midostaurin. Please conduct an indirect comparison between these two treatments for these outcomes, or where not feasible, provide a justification and a narrative summary.

A19 Response: An ITC of QoL between quizartinib and midostaurin was not conducted as evidence for the QoL impact of treatment with midostaurin was not identified in the published literature. Lacking this evidence, an analysis was not deemed feasible.

An ITC of safety outcomes with quizartinib and midostaurin was not conducted given the limited impact of adverse events on cost-effectiveness outcomes. When the adverse event rates for midostaurin were assumed to be equal to those of the quizartinib arm in the QuANTUM-First study the impact on the incremental cost effectiveness ratio (ICER) was found to be limited (company revised base case ICER: £2,970, Scenario analysis ICER: £2,855).

An overview of the adverse event rates is provided in Table 17. It should be noted that while absolute numbers of events differed likely due to differences between the trials (e.g. due to the way adverse events were reported across the trials), both trials indicated that quizartinib and midostaurin had comparable safety profiles to their respective placebo arms. An ITC is therefore expected to provide limited additional evidence.

Table 17. Overview of adverse events in QuANTUM-First and RATIFY

	QuANTUM-First		RATIFY	
	Grade ≥3 treatment-emergent AEs		Summary of Grade 3, 4, or 5 AEs	
	Quizartinib[a]	SC[a]	Midostaurin[b]	Placebo[b]
Anaemia	5.7%	5.2%	92.7%	87.9%
Diarrhoea	3.8%	3.7%	15.8%	15.3%
Fatigue	0.4%	0.0%	9.0%	10.5%
Febrile neutropenia	43.8%	41.0%	81.7%	82.5%
Hyperbilirubinemia	x.x%	x.x%	7.0%	7.9%

	QuANTUM-First		RATIFY	
	Grade ≥3 treatment-emergent AEs		Summary of Grade 3, 4, or 5 AEs	
Hypocalcaemia	0.8%	3.0%	6.8%	5.9%
Hypokalaemia	18.9%	16.4%	13.8%	16.9%
Hyponatraemia	x.x%	x.x%	8.7%	6.5%
Hypophosphataemia	6.8%	6.0%	5.4%	8.2%
Increased alanine aminotransferase	4.5%	4.9%	12.7%	9.3%
Infection	xx.x%	xx.x%	52.4%	50.3%
Leukopenia	x.x%	x.x%	26.2%	29.7%
Lymphopenia	x.x%	x.x%	19.2%	22.0%
Mucositis or stomatitis	4.5%	3.0%	6.2%	7.9%
Nausea	1.5%	1.9%	5.6%	9.6%
Neutropenia	18.1%	8.6%	95.2%	95.8%
Pain	x.x%	x.x%	13.2%	12.4%
Pneumonitis or pulmonary infiltrates	xx.x%	xx.x%	7.9%	8.2%
Rash or desquamation	3.0%	1.1%	14.1%	7.6%
Thrombocytopenia	7.9%	9.7%	97.5%	96.6%
Neutrophil count decreased	8.7%	3.4%	0.0%	0.0%
Sepsis	5.7%	9.7%	0.0%	0.0%
Gamma-glutamyl transferase increased	x.x%	x.x%	0.0%	0.0%
Platelet count decreased	x.x%	x.x%	0.0%	0.0%
Hypertension	4.9%	6.7%	0.0%	0.0%

Abbreviations: AE, adverse event; SC, standard chemotherapy.
References: Erba et al. 2023 (7); Stone et al. 2017 (22)
Notes: a. Data reported in this table includes grade ≥3 treatment-emergent AEs that occurred in ≥ 5% of patients in QuANTUM-First trial (Erba et al. 2023); b. Data reported in this table includes grade 3, 4 or 5 AEs that occurred in ≥ 5% of patients in midostaurin's pivotal trial (RATIFY) reported in Stone et al., 2017.

Quizartinib has a manageable safety profile and life-threatening toxicities are rare; long-term safety data and subgroup analysis did not reveal any safety concerns or patient population at increased risk.

In both QUANTUM-First and RATIFY no grade 3 or 4 treatment-emergent adverse events (TEAEs) had a ≥ 10% difference in incidence rate between treatment and placebo groups (7, 22). In the QuANTUM-First and RATIFY trials an intensive chemotherapy regimen was provided in both the treatment (quizartinib/midostaurin) and placebo arms. A clinical expert advised that serious adverse events (SAEs) are often related to the intensive chemotherapy regimens rather than to the FLT3 inhibitors administered which aligns with the similar adverse event (AE) rates observed between treatment and placebo groups in both RATIFY and QuANTUM-First. The clinical expert also noted that in the clinical setting the AE profile between midostaurin and quizartinib is not very different during the intensive chemotherapy treatment.

The main safety risks for quizartinib were QT prolongation/ventricular arrhythmia, myelosuppression and infection (7). Similarly, in midostaurin treated patients, an increased frequency of corrected QT interval (QTc) prolongation and infection were also notable safety risks (22). Furthermore, the most frequent overall AEs were those associated with myelosuppression and these AEs also comprised the most frequent grade 3-4 AEs (23). Midostaurin has some additional tolerability issues due to the formulation which may cause stomach discomfort and diarrhea. A clinical expert indicated that the AE profile of quizartinib is at worst similar to that of midostaurin, although midostaurin is expected to have worse gastrointestinal side effects.

A20. Section E.1.2.1.3, Appendix E states that there were no clinically meaningful differences in the quizartinib safety profile related to the choice of anthracycline. However, a higher proportion of quizartinib + idarubicin patients had Treatment-emergent adverse events (TEAEs) associated with study treatment dose interruption and study treatment discontinuation compared with quizartinib+daunorubicin. In addition, the proportion of Serious adverse events (SAEs) was higher in the placebo+idarubicin arm. Please comment on these differences.

A20 Response: The TEAE rates for study dose interruption were 17.1% for quizartinib and daunorubicin and 23.1% for quizartinib and idarubicin compared to 8.5% for placebo and daunorubicin and 8.8% for placebo and idarubicin. Similarly, the rates were higher for treatment dose interruption in the quizartinib and anthracycline arms (27.6% for quizartinib and daunorubicin, 39.4% for quizartinib and idarubicin) compared to the placebo and anthracycline arms (20.2% for placebo and daunorubicin, 20.5% for placebo and idarubicin). Overall, the most frequently reported TEAEs associated with treatment interruption or discontinuations in the quizartinib arms were cytopenias and infections. Other causes of drug interruptions with quizartinib were electrocardiogram (ECG) QT prolonged, aspartate aminotransferase (AST) increased, pneumonia, diarrhoea and stomatitis. Sepsis and diarrhoea were the most frequently reported TEAEs associated with study drug interruption in the placebo arm.

A review of TEAEs by choice of anthracycline did not identify any clinically meaningful differences in the safety profile. The type and incidence of TEAEs most frequently reported were similar in the anthracycline subgroups.

Section B: Clarification on cost-effectiveness data

Revised Company Base Case

Company provides a revised base case to correct the errors identified by EAG in the model, which is related to question B16 and B17. More details of the model changes can be found in the responses to these two questions below in (page 97) and (page 98), respectively.

In addition, an error in the calculation of 1L HSCT costs was identified and corrected in the revised base case. A correction was applied in the Patient distribution tab columns AW, DT and GQ to align the proportion of patients entering HSCT 1L with the model trace.

The revised deterministic base case results applying the quizartinib patient access scheme (PAS) price are presented in Table 18. The revised results show that quizartinib is cost-effective when comparing with standard chemotherapy (SC) with an ICER £17,364/ quality adjusted life year (QALY) gained and with midostaurin with an ICER £3,459/QALY gained.

The fully incremental analyses confirm that quizartinib is a cost-effective alternative to midostaurin and SC (Table 19). The results suggest that at a willingness-to-pay (WTP) threshold of £30,000/QALY gained quizartinib is associated with a net population health benefit and is a cost-effective use of NHS resources (Table 20).

Table 18. Incremental cost-effectiveness results (deterministic base-case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,459
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,364

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

Table 19. Fully incremental analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER fully incremental (£/QALY)
SC regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£47,175
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,459

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy
Notes: These results are the results using the quizartinib PAS price.

Table 20. Net health benefit of quizartinib

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000 WTP threshold	NHB at £30,000 WTP threshold
Quizartinib regimen	£xxx,xxx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	£x,xxx	x.xx	1.80	1.93
SC regimen	£xxx,xxx	x.xx	£xx,xxx	x.xx	0.42	1.34

Abbreviations: LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit; SC, standard chemotherapy; WTP, willingness to pay.
Notes: These results are the results using the quizartinib PAS price

All the scenario analysis conducted to responses to EAG questions were based on this revised base case.

Model structure

B1. Priority Question: The EAG considers that the approach to modelling outcomes in patients who have either relapsed or refractory disease (following first-line treatment) is overly complicated and inaccurate. The current approach relies on explicitly modelling transitions (Markov model) and assumes time-invariant transition probabilities. The data to populate this approach is, however, very limited (due to the lack of access to induvial participant data [IPD] from ADMIRAL) and involves making strong assumptions which do not align with the observed data from ADMIRAL.

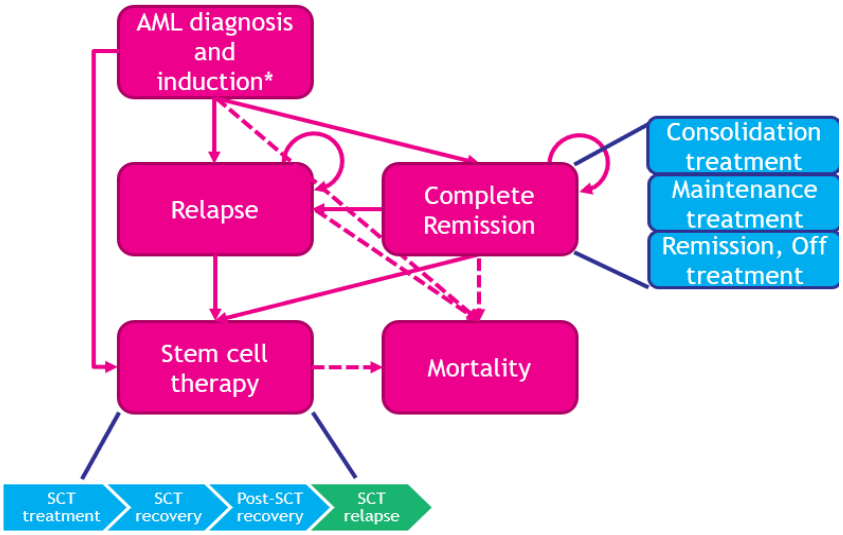
a. **Please justify the adopted modelling and explain why a simpler partition survival model (PSM) was not considered.**

b. **A significant issue with the adopted approach is that it does not allow for cure in patients who achieve remission in a second-line setting. This is clinically unrealistic and contrary to the modelled assumption in technology appraisal (TA) 642. Please justify the current approach to restricting cure to a first-line setting only.**

c. **The EAG highly recommends revising the current model structure to incorporate a nested PSM to reflect outcomes in patients with relapsed and refractory disease. Please present a scenario analysis incorporating a PSM approach.**

B1a Response: An systematic literature review (SLR) of cost-effectiveness studies in FLT3+ AML was conducted to identify published economic evaluations of interventions that could be used to address the NICE decision problem and inform the economic model structure. The SLR identified one UK model of newly diagnosed FLT3+ AML within a NICE submission of a FLT3 inhibitor, midostaurin (TA523). TA523 is a recent submission which employed a partitioned survival model to assess the cost-effectiveness of midostaurin, the most relevant comparator in this appraisal (24) (Figure 39). The model structure for quizartinib was conceptualised based on the model from TA523 considering its critique from the NICE committee.

Figure 39. Partition survival model structure submitted to NICE for the technology appraisal for midostaurin (TA 523)



Abbreviations: SCT, stem cell transplantation
Source: Adapted from NICE TA for midostaurin (24)

Several key issues were reported at the technical engagement stage following the assessment of the midostaurin model by the evidence review group (ERG). Three of these key issues were deemed most relevant for the quizartinib model and were considered during the current model's technical specification phase:

1. Potential of response to subsequent therapy for refractory or relapsed (R/R) patients was not captured

In the midostaurin model submitted to NICE (Figure 39), it did not capture the response to subsequent treatment and allow refractory or relapsed patients to move into CR state. The ERG argued that this had a significant impact on the model leading it to underestimate the incremental cost-effectiveness result.

2. Failure to capture the relapse following HSCT

In the midostaurin model used in the NICE submission (Figure 39), an assumption was made that patients who enter the HSCT health state would either remain in post-HSCT recovery or transition to death. The ERG debated this assumption on the basis that the literature suggests that between 25% to 40% of patients relapse following HSCT. The midostaurin model also failed to consider the lower utility associated with a relapse following HSCT.

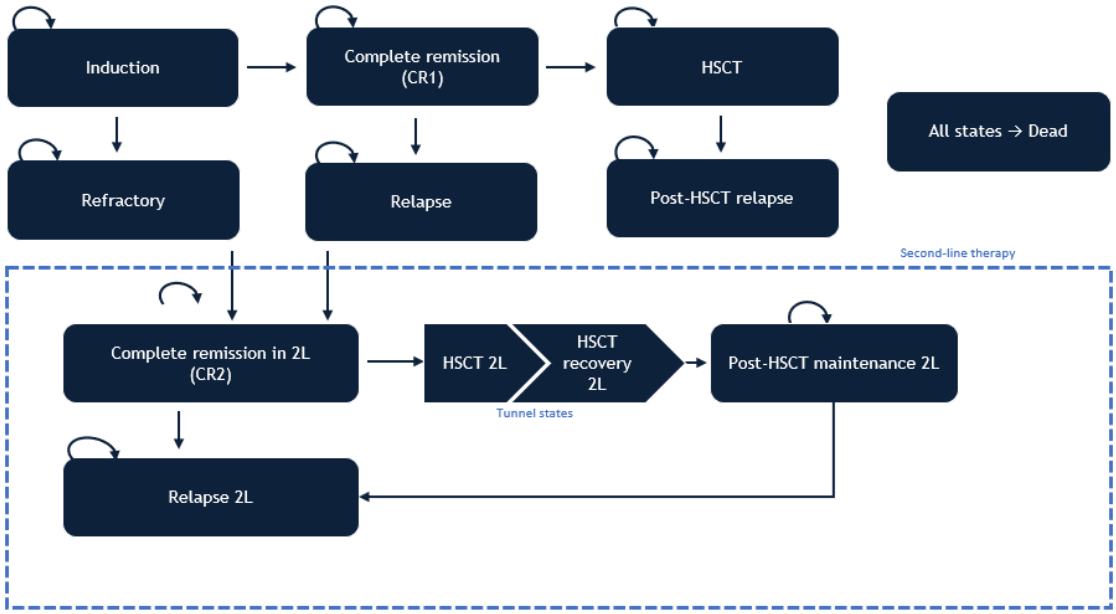
3. Refractory and relapsed patients were not distinguished in the model

In the midostaurin model used in the NICE submission (Figure 39), the ERG noted that patients who fail to respond to induction therapy were grouped together with patients who relapse after achieving CR and as such it was not possible to distinguish between these two groups of patients. The assumption was made that the costs for patients who are primary refractory and patients who relapse were the same.

In addition, state transition models incorporate an explicit link between clinical endpoints. This means that extrapolations depend upon state membership at the end of trial follow-up, the model structure, and within-trial estimates of each transition probability. This allows the prognostic nature of intermediate health states to be reflected in the extrapolation period, and differential treatment effects to be applied to different components of the disease process. It also allows the processes driving extrapolated results to be reviewed and subject to sensitivity analysis (25).

To address the key issues and limitations described by the EAG in TA523, the company has built a state transition model (Figure 40). This model incorporates new health states and integrates historical data through time-dependent transition probabilities and tunnel states.

Figure 40. Model schematic



Abbreviations: HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; CR1, first CR; CR2, second CR first-line treatment; 2L, second-line treatment

Unlike the midostaurin model, 2L (second-line) treatment for R/R is comprehensively modelled. An additional health state, CR 2, has been introduced to prevent patients on subsequent treatment from remaining in the relapse state until death or HSCT. This addition enables the model to differentiate between patients who respond to 2L treatment and those who do not, considering factors such as costs, QALYs, and disease progression. Patients who achieve CR after subsequent therapies (i.e. CR 2) are then also eligible for HSCT. Patients who relapse in CR 2 before receiving HSCT enter a 2L relapse state (i.e. relapse 2L).

The quizartinib model has been enhanced with another additional health state, post-HSCT relapse, to account for patients who relapse after HSCT. Notably, patients who relapse after HSCT 1L do not enter the same relapse state as those who relapse out of first-line care, and they are ineligible for a second HSCT.

The model also accommodates separate health states for relapse patients and primary refractory patients. This allows the model to capture different costs for these distinct groups of patients.

B1b Response: In line with previous technology appraisals (Tas) in AML (26-28), cure was applied in cost effectiveness models (CEM) for 1L patients. It was assumed that patients who did not experience disease progression for a period of 3 years as being cured. Since all patients in 1L enter the model at time zero, it is straightforward to ascertain the proportion of patients that did not experience disease progression by any time point (3 years in the base case). However, patients can progress from 1L treatment at cycle, therefore, the model has no memory of how long each cohort of “new progressors” spends in second remission (CR2). Applying cure in 2L would require tracking each cohort of patients as they enter 2L. Considering the granularity of the CEM health states in 2L treatment, this would require a very high number of tunnel states, greatly increasing the model complexity.

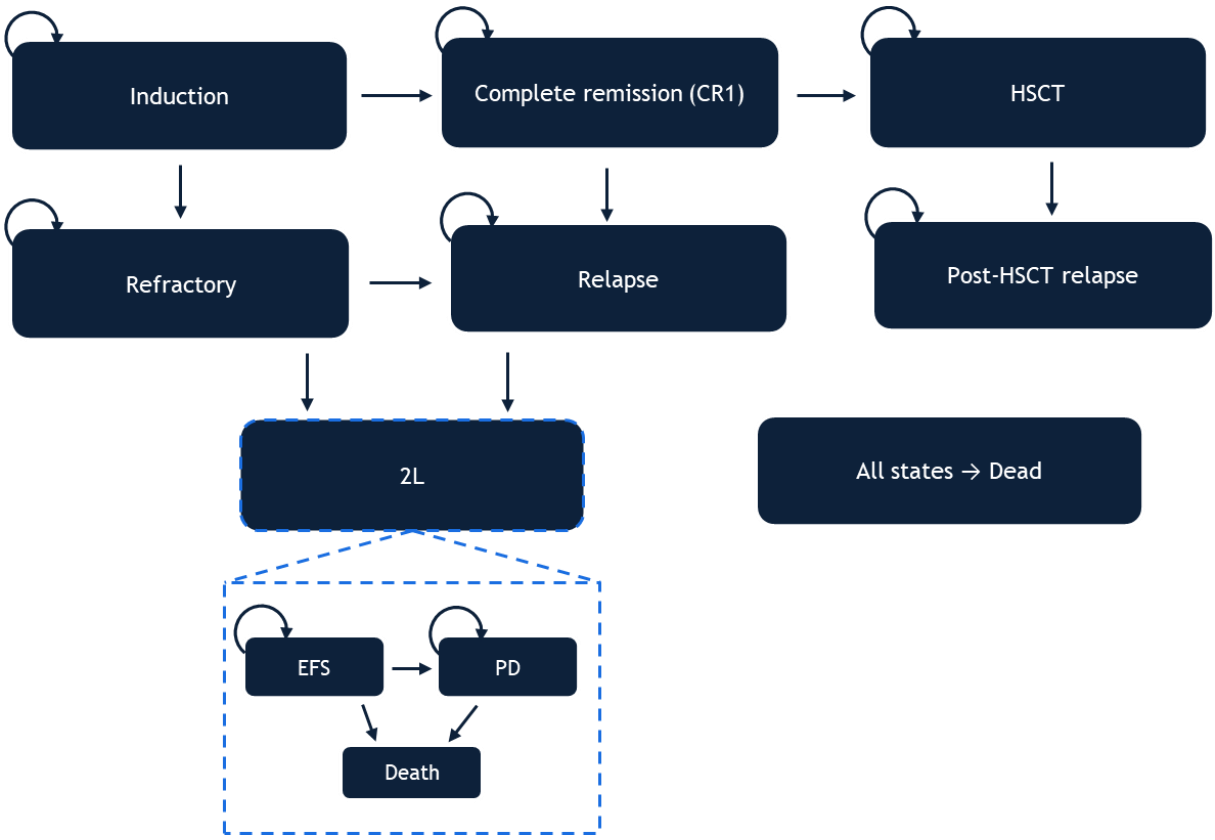
Therefore, the choice was made to develop the model with granular health states in 2L, at the expense of excluding cure in the 2L setting. Since QALY gain in 2L is 12%, 31% and 25% of the total for quizartinib, SC and midostaurin, respectively (from the revised base case), it is expected that cure in 2L would have a modest impact on the

model outcomes and would not change the cost-effectiveness conclusions from the base case.

To test this hypothesis, a scenario applying cure in 2L was conducted in the version of the CEM with a nested PSM for 2L outcomes (B1c), as this approach enabled a relatively straightforward way to apply cure, albeit with some limitations. The methods and results for this scenario analysis are provided in the reply to question B1c. In summary, applying cure in 2L resulted in a higher ICER, but the increase was relatively minor (vs. midostaurin from £311 to £1,773, vs. SC from £16,867 to £18,098; Table 28). More details can be found in the responses to question B1c below.

B1c Response: The CEM was updated to replace all health states after disease progression in 1L with a nested PSM informed by EFS and OS data from the Admiral trial. Hence, all model health states post disease progression (refractory, relapse, CR2, HSCT 2L, HSCT recovery 2L, post-HSCT maintenance 2L and relapse 2L) were replaced by a single health state (2L), as shown in Figure 41.

Figure 41. Model structure



Abbreviations: 2L, Second-Line; CR, Complete Response; EFS, Event-Free Survival; HSCT, Hematopoietic Stem Cell Transplantation; PD, Progressive Disease.

In the updated model structure, patients transition from the induction and CR1 health states directly into the 2L health state with the survival in this health state estimated with OS from the ADMIRAL trial. The model captures and follows each cohort of patients entering the 2L health state in each cycle using tunnel states. This technique allows the model to track the survival of each cohort using the OS curve for 2L, from the ADMIRAL trial.

In turn, the outcomes (LYs, QALYs and costs) for the 2L health state are estimated using the nested PSM. In the PSM, lifetime outcomes for patients entering 2L are estimated using EFS and OS curves from the ADMIRAL trial. The lifetime outcomes estimated in the PSM are then frontloaded as a fixed pay-off for each cohort patients entering the 2L health state.

Considering the EAG feedback and request in question B15b, 2L EFS and OS curves for quizartinib, SC and midostaurin were all constructed using a blended survival curve (i.e. the survival curves in ADMIRAL for gilteritinib and salvage chemotherapy were weighted by the proportion of patients receiving each subsequent treatment). The distribution of subsequent treatments used in these analyses are consistent with the company base case values (Table 21).

Table 21. Distribution of subsequent treatments

Treatment	2L treatment distribution according to 1L treatment choice		
	Quizartinib	SC	Midostaurin
FLAG-Ida	60%	50%	40%
Gilteritinib	40%	50%	60%

Abbreviations: 1L, first-line treatment; 2L, second-line treatment; FLAG-Ida, fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; SC, standard chemotherapy.

Inputs and assumptions for 2L nested PSM

ADMIRAL trial survival analyses

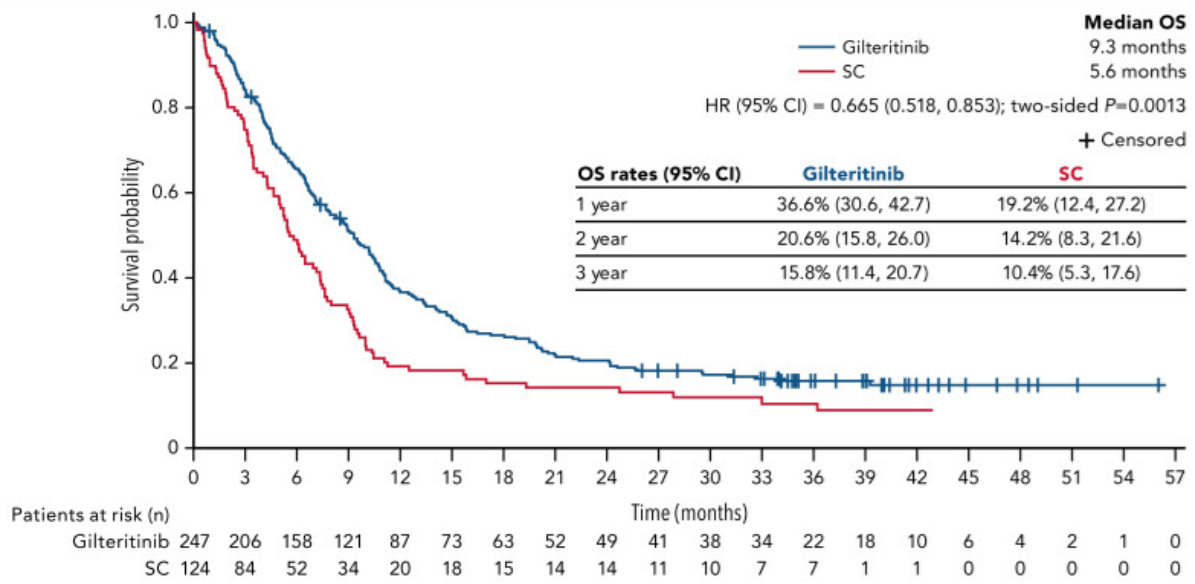
To inform the 2L PSM model (and survival for patients entering 2L), it was necessary to reconstruct and extrapolate EFS and OS curves from the ADMIRAL trial. EFS was selected as the endpoint to model disease progression in 2L as this was the only endpoint relevant for the model available in the literature for both gilteritinib and salvage chemotherapy (RFS not reported and CIR only available for gilteritinib).

Independent parametric models were fit to gilteritinib and salvage chemotherapy arms.

OS

KM data for OS was sourced from Perl et. al. 2022 (29) and is presented in Figure 42. KM data was digitised and reconstructed using the IPDfromKM R package (27).

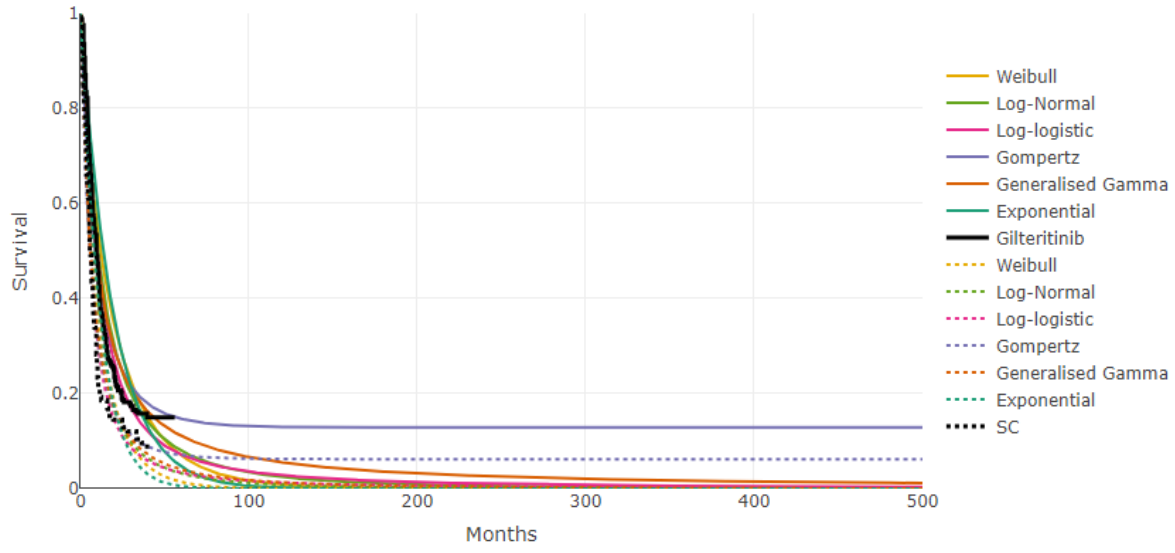
Figure 42. OS data from the ADMIRAL trial



Abbreviations: HR, hazard ratio; OS, overall survival; SC, salvage chemotherapy.

The overlay of the reconstructed KM data and parametric extrapolations is presented in Figure 43.

Figure 43. Independent models for OS in 2L



Abbreviations: SC, standard chemotherapy.

The best fitting curves were selected based on Akaike information criterion (AIC)/Bayesian information criterion (BIC) scores, presented in Table 22.

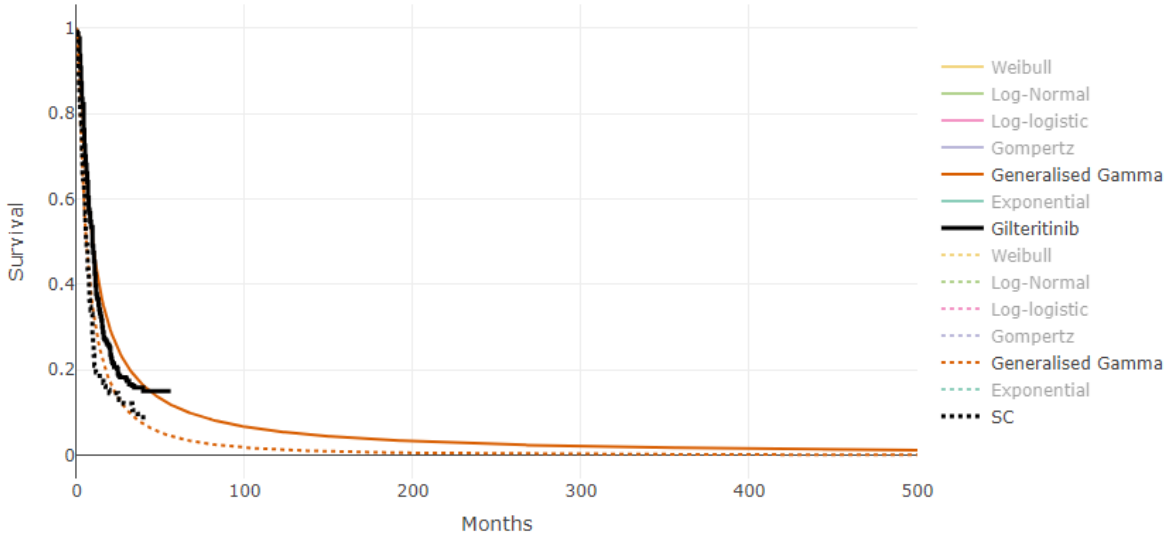
Table 22. AIC and BIC scores for independent models of OS

Distribution	Gilteritinib		Salvage chemotherapy	
	AIC	BIC	AIC	BIC
Generalized Gamma	1587.67	1598.2	752.9	761.37
Log-logistic	1596.78	1603.8	747.39	753.03
Log-Normal	1601.26	1608.28	751.67	757.31
Gompertz	1603.8	1610.81	754.12	759.76
Weibull	1660.93	1667.95	774.7	780.34
Exponential	1670.78	1674.29	778.7	781.52

Abbreviations: AIC; akaike information criterion; BIC; bayesian information criterion; OS, overall survival.

Generalised gamma was the model with the lowest AIC/BIC for the gilteritinib arm, therefore it was selected for the analyses. For salvage chemotherapy, generalised gamma was only the 3rd best fitting model however, for consistency between the treatment arms in the ADMIRAL trial, generalised gamma was also selected. It should be noted that all parametric models (except Gompertz) fitted to the salvage chemotherapy arm result in similar mean survival (restricted mean to the model time horizon), therefore the curve choice has minimal impact of the model outcomes. The resultant OS curves used in the CEM are provided in Figure 44.

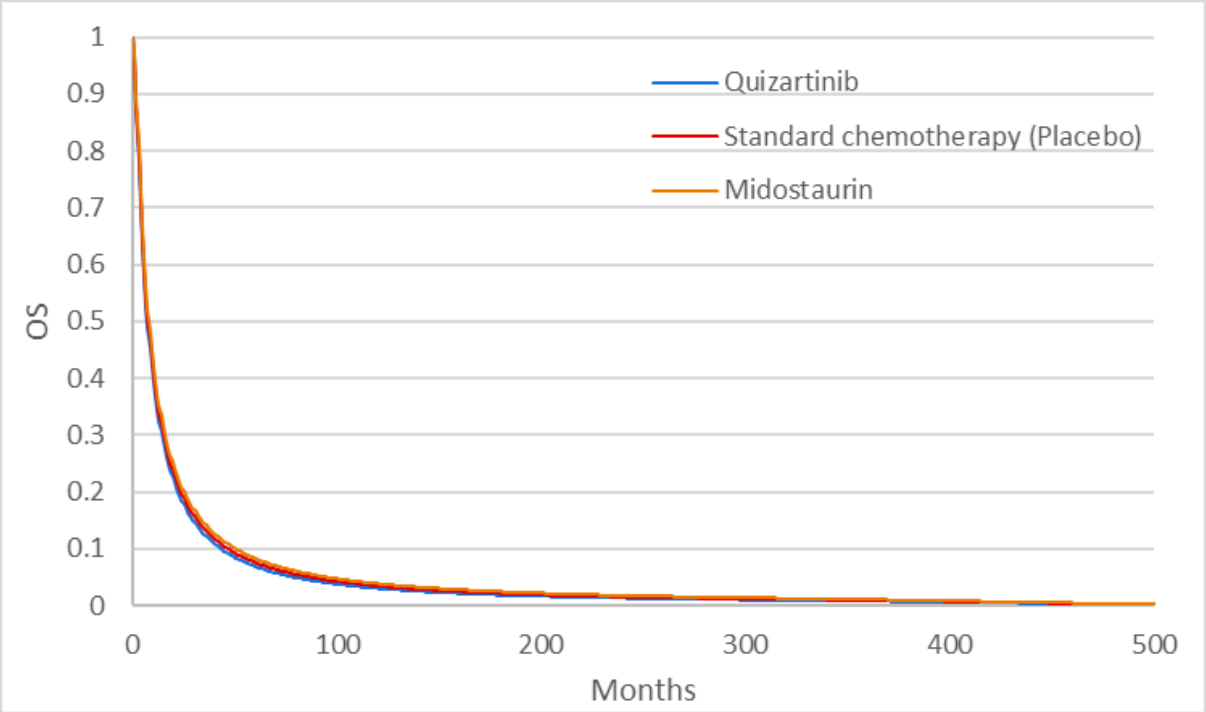
Figure 44. Selected models of OS in 2L



Abbreviations: SC, standard chemotherapy.

The blended survival curves applied in the CEM (weighted by the proportion of patients receiving each subsequent treatment and adjusted for general population mortality) for quizartinib, SC, and midostaurin are presented in Figure 45.

Figure 45. Blended OS curves used in the CEM

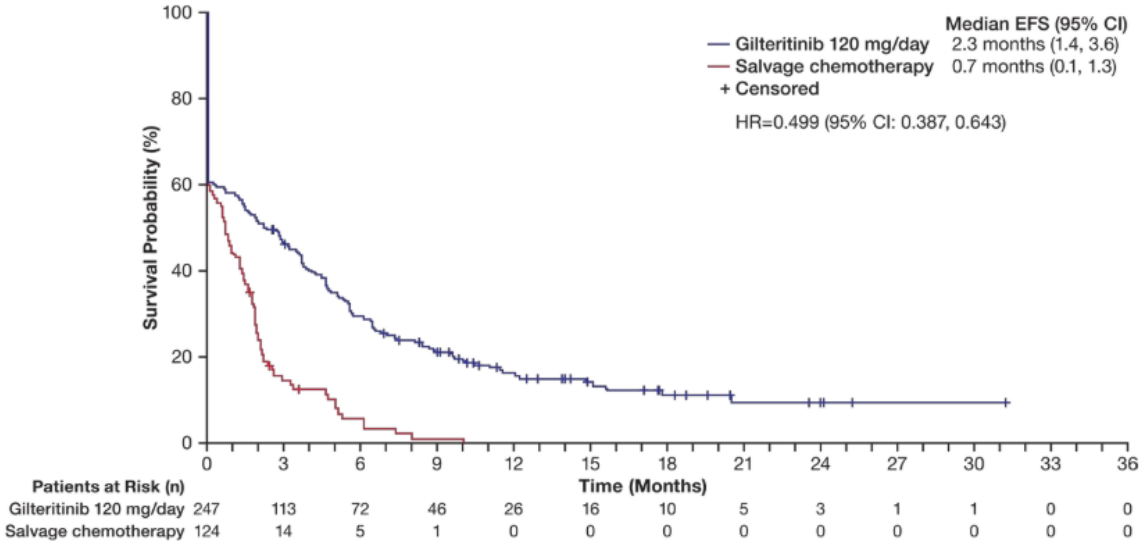


Abbreviations: CEM, cost-effectiveness model; OS, overall survival.

EFS

KM data for EFS was sourced from Perl et. al. 2019 (30) and is presented in Figure 46. EFS was defined as a failure to obtain CRc with failures assigned as an event on randomization, relapse, or death from any cause, including events and initiation of new anti-leukaemia treatments reported in long-term follow up.

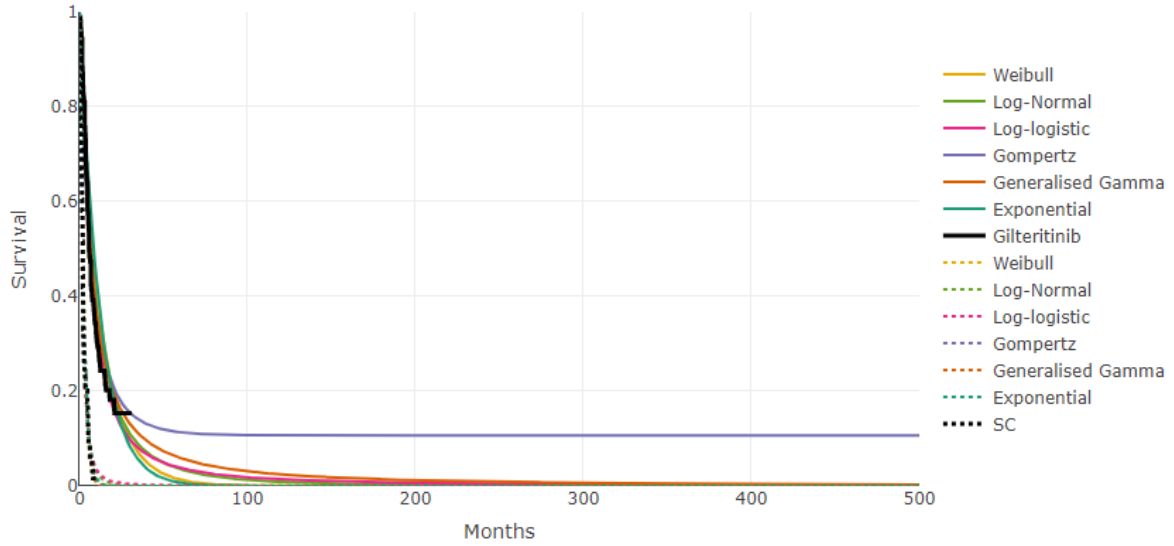
Figure 46. EFS data from the ADMIRAL trial



Abbreviations: EFS, event free survival; HR, hazard ratio.

Due the EFS definition, the curves drop sharply at time 0, making it difficult to fit a standard parametric model to the data. Therefore, EFS extrapolations were conducted using truncated and rebased curves (i.e., only for patients who achieve CRc). The EFS curve was then manually adjusted in the CEM to reflect the drop at time 0. The overlay of the reconstructed KM data and parametric extrapolations is presented in Figure 47.

Figure 47. Independent models for EFS in 2L



Abbreviations: EFS, event free survival; SC, standard chemotherapy.

The best fitting curves were selected based on AIC criteria, presented in Table 23.

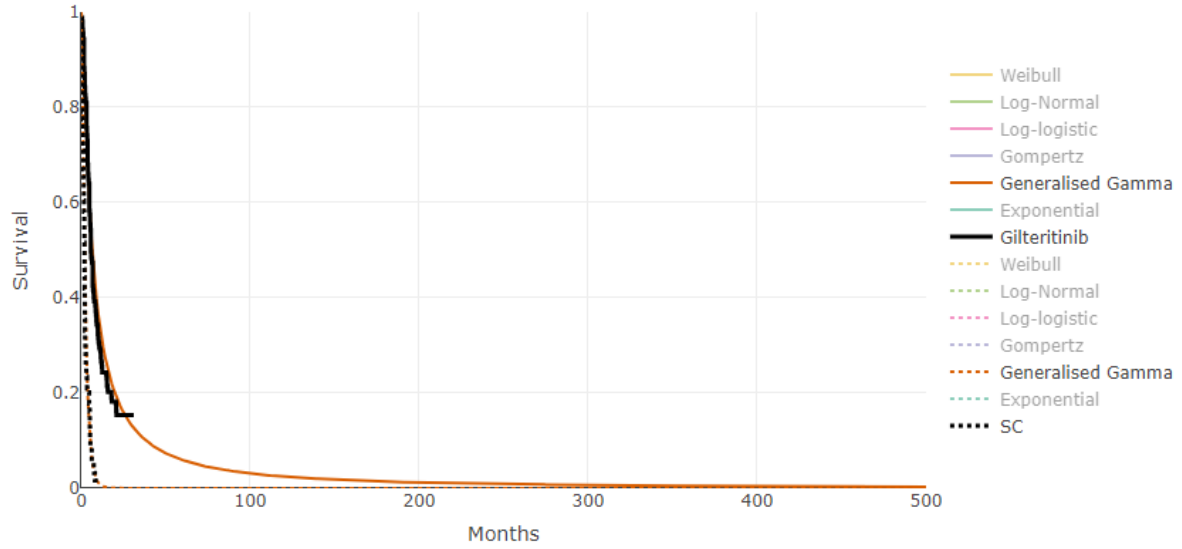
Table 23. AIC and BIC scores for independent models of EFS

Distribution	Gilteritinib		Salvage chemotherapy	
	AIC	BIC	AIC	BIC
Generalized Gamma	1407.18	1417.7	465.06	473.52
Log-logistic	1408.33	1415.35	465.94	471.58
Log-Normal	1412.15	1419.17	470.93	476.57
Gompertz	1424.79	1431.81	472.12	477.76
Weibull	1460.45	1467.47	466.67	472.32
Exponential	1462.34	1465.85	472.32	475.14

Abbreviations: AIC; akaike information criterion; BIC; bayesian information criterion; EFS, event free survival.

Generalised gamma was the model with the lowest AIC for both treatment arms, therefore it was selected for the analyses. Similar to OS, all parametric models fitted to EFS data for the salvage chemotherapy arm result in similar mean survival (restricted mean to the model time horizon), therefore the curve choice has minimal impact of the model outcomes. The resultant EFS curves used in the CEM are provided in Figure 48.

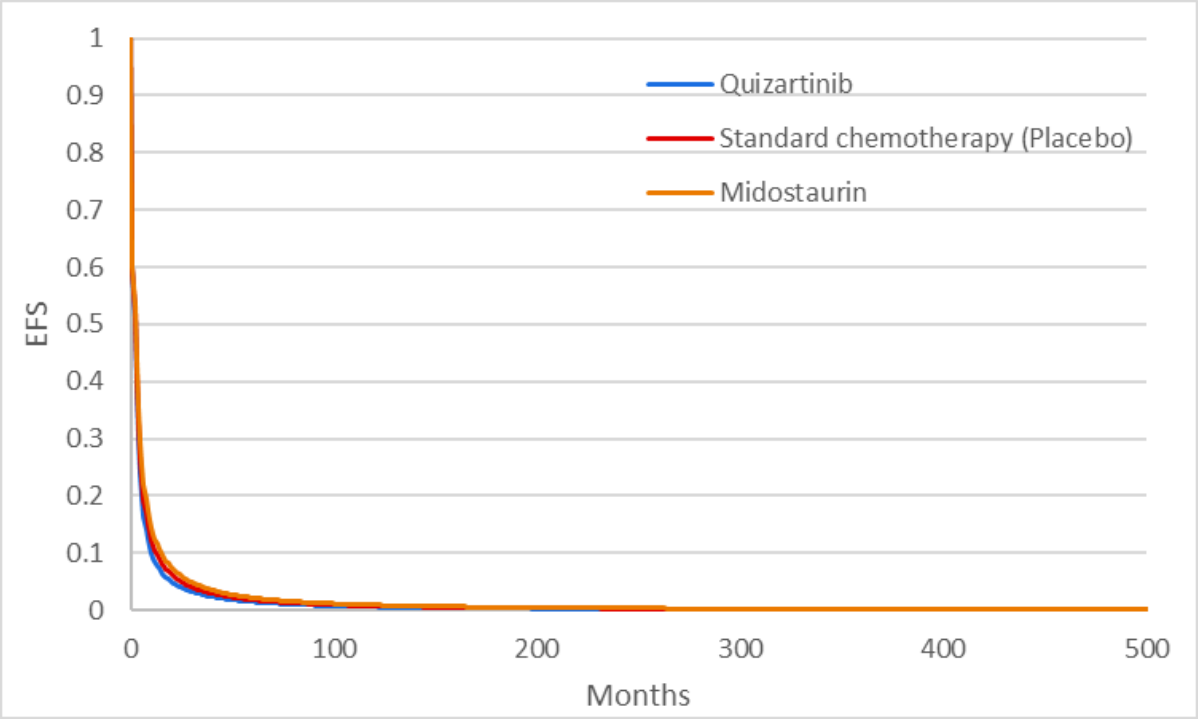
Figure 48. Best fitting models for EFS in 2L



Abbreviations: 2L, second line; EFS, event free survival; SC, standard chemotherapy.

The final EFS curves applied in the CEM (including the manual adjustment for the drop at time 0, weighted by the proportion of patients receiving each subsequent treatment and adjusted for general population mortality) are presented in Figure 49

Figure 49. Blended EFS curves applied in the CEM



Abbreviations: CEM, cost-effectiveness model; EFS, event-free survival.

Health-related quality-of-life inputs

To estimate the QALY pay-off for patients entering the 2L health state in the CEM, utilities for the EFS and progressed disease health states in 2L were necessary. The utility values were selected from the original model health states to best match the disease state in the nested PSM. The utility values used for the 2L PSM are presented in Table 24.

Table 24. Utility values used in the 2L PSM

Health state (2L PSM)	Corresponding health state in original model	Utility value
EFS	CR2	0.747
PD	Relapse 2	0.477

Abbreviations: 2L, second line; CR2, complete remission in second line; EFS, event free survival; PD, progressive disease; PSM, partitioned survival model.

Costs inputs

Costs categories included in the 2L PSM are the same as in the original model (drug acquisition and administration, monitoring, disease management and 2L HSCT procedure)

Treatment costs in 2L for the gilteritinib arm were estimated applying the drug acquisition, administration, and monitoring costs per cycle for all patients in the EFS

health state (i.e., treatment until disease progression). For the fludarabine, cytarabine, idarubicin and granulocyte colony stimulating (FLAG-IDA) arm, 1 treatment cycle was assumed, as per the original model assumptions. Patients in the PD health state only accrued disease management costs.

Similar to utilities, disease management costs were selected from the original model health states that better match the disease state in the nested PSM. The disease management costs used in the 2L PSM are presented in Table 25.

Table 25. Disease management costs applied in the 2L PSM

Health state (2L PSM)	Corresponding health state in original model	Disease management cost
EFS	CR2	£457
PD	Relapse 2	£2,389

Abbreviations: 2L, second line; CR2, complete remission in second line; EFS, event free survival; PD, progressive disease; PSM, partitioned survival model.

While the 2L PSM does not explicitly model HSCT, a proportion of patients in the ADMIRAL trial received the procedure therefore this is implicitly captured in the survival curves. Costs of HSCT in 2L were estimated using the same unit cost as 1L HSCT and the proportion of patients receiving HSCT in the ADMIRAL trial (weighted average between 2L treatment arms and 1L subsequent treatment distribution). The proportion of patients receiving HSCT in the ADMIRAL trial was sourced from Pearl et. al. 2019 (30) (Table 26)

Table 26. Proportion of patients receiving HSCT in the ADMIRAL trial

Treatment	Proportion of patients receiving HSCT
Gilteritinib	26%
Salvage chemotherapy	15%

Abbreviations: HSCT, allogeneic haematopoietic stem cell transplant.

Results

The results of 2L nested PSM model was presented in Table 27. It should be noted that these results were based on the revised company base case, which include the corrections for questions 16 and 17.

Table 27. Scenario analysis supporting B1c

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£xxx	x.xx	x.xx	£311
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£16,867

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

The results show that adopting a nested PSM approach to model 2L outcomes results in a lower ICER for quizartinib versus midostaurin and SC, compared with the revised base case in the company model.

Cure in 2L (related to question B1b)

As mentioned in the reply to question B1b, implementing 2L cure was not feasible in the original model structure. However, the 2L PSM approach allowed for a relatively straightforward method to implement cure in 2L, therefore, a supporting scenario analyses was conducted using this approach. The effect of 2L cure can therefore be evaluated by comparing the results of the PSM approach with and without 2L cure.

Cure in 2L was implemented according to the same principles applied in 1L.

Regarding costs and utilities, after a period of 3 years (from the time of 1L disease progression), patients remaining in the EFS health state did not accrue any treatment, monitoring and disease management costs. In addition, following cure, utilities from the general population were assumed for EFS.

As for survival, similarly to 1L, it was assumed that, after cure, EFS patients could no longer experience disease progression. Furthermore, after the cure point, OS was set to the standard mortality ratio (SMR) adjusted general population mortality.

It should be noted that the PSM approach still does not allow a completely accurate implementation of cure in 2L, as OS is not differentiated between EFS and PD patients (differentiating survival of EFS and PD patients would require a semi-Markov approach for the 2L nested model). Therefore, setting OS to the SMR adjusted general population mortality overestimates the effect of cure, since mortality risk is also reduced for patients that already progressed.

Inspection of the EFS curves (Figure 49) shows that most patients experienced disease progression by year 3 therefore, it can be argued that it would be preferable

to omit the OS adjustment. However, for the purpose of this scenario (i.e., evaluating the impact of cure in 2L), we deemed that it would be more informative to overestimate rather than underestimate the effect of cure. This is because cure in 2L is likely to provide a higher benefit for the 1L therapies with higher relapse rates (i.e. SC and midostaurin).

The results of 2L nested PSM with cure are presented in Table 28.

Table 28. Scenario analysis supporting B1b

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	0	0	0	0
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£1,773
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£18,098

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

As expected, including cure in 2L results in worse outcomes for quizartinib due to lower proportion of patients reaching 2L. However, even overestimating cure in 2L results in only a modest increase in the ICER of quizartinib versus midostaurin and SC, reinforcing the validity of the assumption that 2L cure has a limited impact of the model outcomes.

B2. Priority Question: Table 1 reports a landmark analysis of overall survival from the QuANTUM-First trial and economic model. The results show that the model predictions do not align with observed data even when the model is calibrated to use unadjusted QuANTUM-First population and KM data from the trial. Please explain this variation.

Table 29 Landmark analysis of overall survival

	QuANTUM-FIRST (unadjusted)[a]		Base case model[b]		Direct comparison using KM[c]	
Statistics	**Quizartinib**	**Placebo**	**Quizartinib**	**Placebo**	**Quizartinib**	**Placebo**
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: a. CS, Table 12. b. company base case assumptions. c. direct pairwise comparison with the survival curves for relapse-free survival after CRc, overall survival after CRc and post-HSCT survival set to KM + Survival model.

B2 Response: The OS (unadjusted) from QuANTUM-First was not directly used in the model based on the model structure shown in Figure 41. Instead, the 'Death from CRc, censored at the start date of all HSCT and relapse' sourced from QuANTUM-First was used to inform the transition from CR1 to death (21). These were estimated based on the time between the date patients enter first CRc and the date of death due to any cause. Patients who relapse or receive HSCT were censored, and patients who did not progress, die, or receive HSCT were censored on the last known date alive.

In addition to the Death from CRc, Induction to Dead, Relapse to Dead, HSCT 1L to Dead, Post HSCT relapse 1L to Dead were also sourced from QuANTUM-First. However, Refractory to Dead and CR2 to Dead for the patients in 2L setting were sourced from the ADMIRAL trial (30).

In addition, a three-year cure point was also applied in the model where a two-fold Standardized Mortality Ratio (SMR) was applied to the general population mortality data to calculate the post-cure mortality (31).

Hence, these OS values would not be expected to align.

B3. Priority Question: The proportion of patients achieving CRc in the model does not align with the efficacy data. Reported Data from QuANTUM-First (unadjusted) states that 71.6% in the quizartinib arm and [redacted] in the placebo arm (CS, Table 11); this does not match the model which shows [redacted] and 64.2% for quizartinib and placebo, respectively (model set to direct comparison). Please explain why these proportions differ from the observed data.

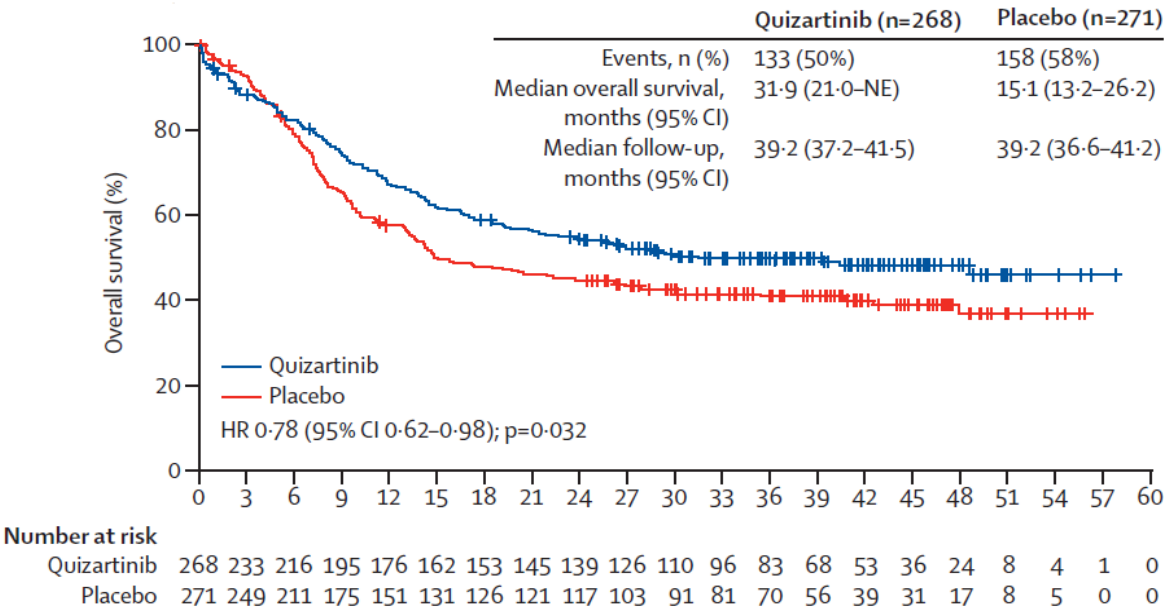
B3 Response: In the QuANTUM-First study, some patients experienced multiple outcomes within the induction period. However, the model does not have the capacity to account for multiple outcomes within the same cycle. Specifically, in the QuANTUM-First study, four patients in the quizartinib group and two patients in the placebo group who achieved CRc also experienced a second outcome, namely death, during the induction period. In the model, these patients do not initially transition into CRc health state. Instead, they transition directly to the health state that corresponds to their final outcome (death) at the end of the induction period in QuANTUM-First. This explains why the inputs used in the model differ from the observed data.

B4. A cure point is applied to patients who remain in the CR1 and PostHSCT maintenance 1L health states beyond three years. Evidence from the RATIFY trial(22) and the AMLSG 16-10 single-arm trial(18) with a median follow-up of 59 months and 40.4 months respectively, suggests that relapse events and mortality continue to occur after 3 years. Please provide further clinical rationale for the assumptions associated with the cure point at 3 years and the absence of relapse beyond this point.

B4 Response: There is no universal consensus on the cure point in AML according to previous NICE TAs. In TA523 for midostaurin (26), the company used a cure point of approximately 6.2 years in the base case, based on the duration of RATIFY. However, according to clinical experts, they anticipate that any individual whose disease remains in remission after five years would be considered cured. In TA642 for gilteritinib (27) in treating R/R patients, the committee accepted a cure point between 2 and 3. In TA787 for venetoclax (28) in treating 1L AML patients who are not suitable for intensive chemotherapy, the company's original model selected a 2-year cure point. However, cure points from 3-5 years were tested in the scenario by the company and EAG. The committee for previous TAs concluded that the evidence supporting any particular cure point selection in the model remains uncertain.

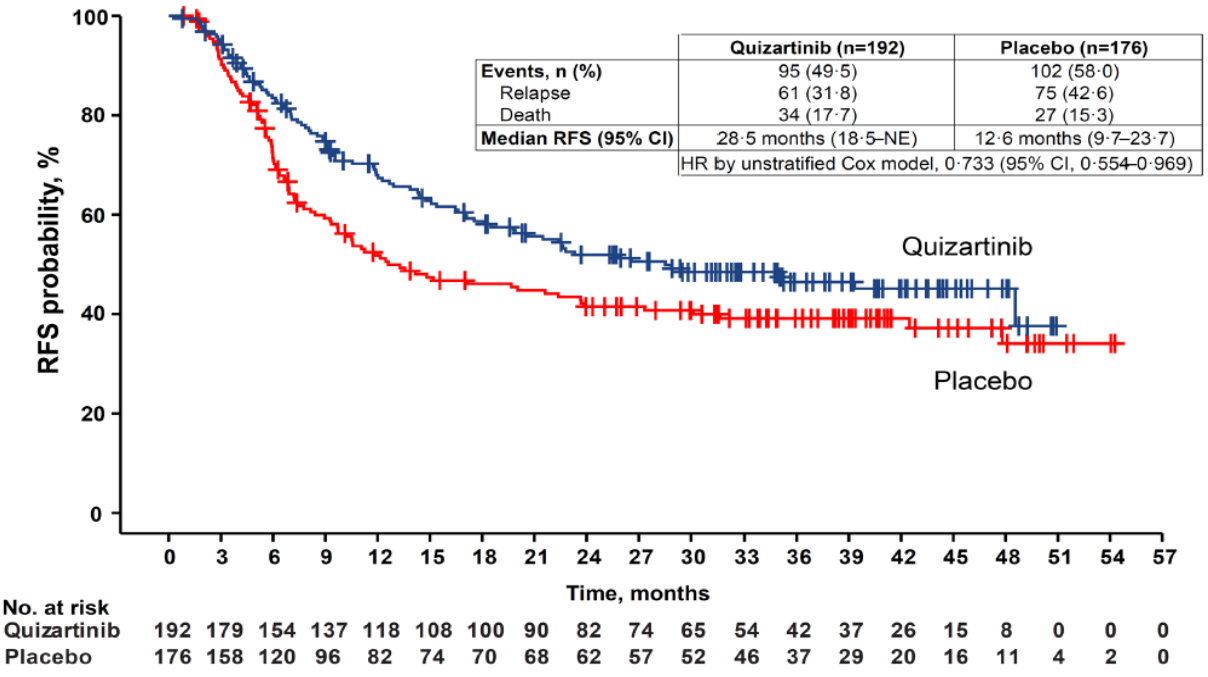
In the company submitted base case selected a three-year cure point. This assumption was based on the observation that the QuANTUM-First OS and RFS curves flattened at this point (see Figure 50 and Figure 51). UK clinical experts consulted also validated this cure point, as they believe it is rare for stable patients to not be considered cured after three years in clinical practice, the point of discharge (32).

Figure 50. Kaplan-Meier plot of overall survival (ITT analysis set)



Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable.
References: Erba et al. 2023 (33)
Notes: Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test. Data cut-off date: 13 Aug 2021

Figure 51. Kaplan-Meier plot of relapse-free survival for subjects who achieved CRc in induction phase – IRC assessment (ITT analysis set)



Abbreviations: CI, confidence interval; CRc, composite complete remission; HR, hazard ratio; IRC, Independent Review Committee; NE, not estimable; RFS, relapse-free survival.
References: Erba et al. 2023 (33)
Notes: Plus symbols indicate censored data. Data cut-off date: 13 Aug 2021

To evaluate the uncertainty of the cure point, extensive scenario analyses were conducted to test the model's sensitivity to the time point assumed for cure (CS Section B.3.9.3, Table 93). These two scenarios were re-conducted based on the Revised Company Base Case and presented in Table 30. In the comparison of quizartinib vs. midostaurin, a cure point of five years resulted in a very similar ICER compared to the base case and a cure point of two years resulted in a slightly higher ICER compared to the base case. In the analysis of quizartinib vs. SC, the ICERs were slighted increased at both alternative cure points compared with the revised base case.

Table 30. Scenario analysis 1 supporting B4

Description		vs. midostaurin			vs. SC		
		Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
Company Revise Base case		£x,xxx	x.xx	£3,459	£xx,xxx	x.xx	£17,364
Alternative cure point:	5 years	£x,xxx	x.xx	£3,229	£xx,xxx	x.xx	£18,345
	2 years	£x,xxx	x.xx	£4,385	£xx,xxx	x.xx	£17,659

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr. incremental; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

Cure was implemented by setting the probability of relapse from these health states to zero (i.e. RFS was assumed to remain constant until death) based on the definition of cure as applied in the base case for 1L. This approach was also in line with prior TAs in AML (TA523, TA642 and TA787) (28, 34, 35) and validated by the key opinion leaders (KOLs) opinion (32). This assumption was also supported by literature, which demonstrated that out of all the relapse cases following HSCT, only a very few patients relapse accrued after three years (13/142, 9.2%) (36).

A scenario analysis was conducted, allowing patients transition from CR1 and HSCT 1L health state to relapse health states after reaching the cure (Table 31). The SMR assumption was unchanged. Compared with the revised base case presented above, the ICERs were only slightly increased when compared with midostaurin (£3,459/QALY gained vs £3,597/QALY gained) and SC (£17,364/QALY gained vs £24,125/QALY gained).

Table 31. Scenario analysis 2 supporting B4

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,597
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£24,125

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

Treatment effect

B5. Priority Question: The base case analysis predicts that [redacted] of patients will proceed to receive a second induction in the quizartinib arm and [redacted] in the SC arm. This contrasts with the [redacted] and [redacted] respectively observed in the QuANTUM-FIRST trial. The EAG believes this discrepancy may be due to how the 1st round induction is modelled, aiming to align the modelled transition probabilities with cycle length.

a. **Please confirm the reason for this discrepancy between the model predictions and observed data.**

b. **Please provide a scenario analysis in which transition probabilities in the 1st and 2nd induction health states are updated to align with observed data. The EAG acknowledges that this may mean that there is a discrepancy between the modelled cycle length and time as observed in the trial.**

B5a Response: The discrepancy between the model predictions and the observed data can be attributed to the assumptions made to synchronize the timelines in the QuANTUM-First trial data with the model's cycle length.

In the QuANTUM-First trial, each induction cycle was allowed to last 28 days, with a margin of ±3 days, whereas the model was designed with a 28-day cycle length.

For the model inputs, it was presumed that the initial 28 days of the trial data corresponded to the first induction cycle of the model. The remaining data was assumed to relate to the second induction cycle of the model. Consequently, patients

who remained in the first cycle of induction beyond the day 28 in the QuANTUM-First study were considered to be in the second induction cycle in the model. This assumption resulted in an increased proportion of patients receiving a second induction cycle in the model compared to the trial data.

B5b Response: A scenario analysis was conducted to align with observed data in the QuANTUM-FIRST as suggested by EAG. According to the model design, the patients who underwent a second induction were considered as residual value (i.e., calculated as 1 – transition probability (TP) from induction to CR1 – tp from induction to Refractory – tp from induction to Death). Consequently, the percentage of patients who underwent a second induction cannot be directly applied in the model. Therefore, the tp from induction to CR1 was calibrated to target xx.x% and xx.x% of patients receiving a second induction in the quizartinib arm and SC arm, respectively. The inputs for this scenario analysis are presented in Table **32**.

Table 32. Transition probabilities from induction round 1 to CR1 inputs in company base case and scenario analysis supporting question B5

	Transition probability, %					
	Quizartinib regimen		SC regimen		Midostaurin regimen	
	Inputs	Reference[a]	Inputs	Reference[a]	Inputs	Reference
Company original base case inputs	xx.x	Weighted population (xx.x of xx.x patients had CRc within 28 days)	xx.x	Weighted population (xx.x of xx.x patients had CRc within 28 days)	xx.x	Based on the MAIC analysis (OR vs quizartinib= x.xx)
Scenario analysis supporting B5b inputs	xx.x	Calibrated to the targeted xx.x% patients received a second induction in quizartinib arm in the Q-F	xx.x	Calibrated to the targeted xx.x% patients received a second induction in SC arm in the Q-F	xx.x	

Abbreviations: CR, complete remission; CR1, first CR; DSE, Daiichi Sankyo Europe; DOF, data on file; HSCT, haematopoietic stem cell transplantation; ITT, intent-to-treat; OS, overall survival; Q-F, QuANTUM First; SC, standard chemotherapy.
Reference: Daiichi Sankyo, 2022 (37); Daiichi Sankyo, 2022 (21)

The results of this scenario analysis were presented in Table 33. Compared with the Revised Base Case, the ICERs were similar for the comparisons against midostaurin (£3,459/QALY gained vs £3,497/QALY gained) and SC (£17,364/QALY gained vs £16,165/QALY gained).

Table 33. Scenario analysis supporting B5b

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,497
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,165

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

As described in the responses to question B5a and acknowledged by EAG, this discrepancy between the trial data and model predictions is attributed to the difference between the time as observed in the trial and modelled cycle length. The scenario analysis demonstrated a limited impact of these inputs in the model.

B6. Priority Question: The base case economic analysis applies parametric extrapolations to post-HSCT survival. The preferred parametric models assume a different function for quizartinib than applied to SC. This is highly unusual and does not align with the recommendations in NICE DSU TSD 14.(38) Further, TSD 14 outlines that where different parametric functions are used this should be carefully justified. Please justify this approach and its clinical plausibility. Additionally, please provide appropriate statistical analysis to support this approach e.g. comparison of hazard trends.

B6 Response: Although the PH assumption (PHA) holds for the post-HSCT survival curves based on the PHA statistical test, independent models were chosen to use to better fit each dataset.

Scenario analyses have been provided in the CS document, Section 3.9.3, where the same parametric model has been applied to both quizartinib and the SC arm. The results of scenario analysis based on the revised base case has been presented in Table 34.

These scenarios resulted in small variations from the base case results, with ICERs varying from £3,483/QALY gained to £3,819/QALY gained vs. midostaurin and ICERs varying from £17,135/QALY gained to £17,422/QALY gained vs. SC. The low sensitivity of the model outcomes despite the wide variations in the different parametric models are due to the assumption of functional cure after 3 years. This restricts the

time frame in which the parametric models are applied, since SMR adjusted general population mortality is used after the cure point.

Table 34. CS scenario analyses results – scenario 12-17

Description	vs. midostaurin			vs. SC		
	Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
Base case	£x,xxx	x.xx	£3,459	£xx,xxx	x.xx	£17,364
Log-logistic	£x,xxx	x.xx	£3,483	£xx,xxx	x.xx	£17,135
Exponential	£x,xxx	x.xx	£3,616	£xx,xxx	x.xx	£17,434
Weibull	£x,xxx	x.xx	£3,605	£xx,xxx	x.xx	£17,562
Log-normal	£x,xxx	x.xx	£3,819	£xx,xxx	x.xx	£18,536
Gamma	£x,xxx	x.xx	£3,589	£xx,xxx	x.xx	£17,390
Gen gamma	£x,xxx	x.xx	£3,557	£xx,xxx	x.xx	£17,366
Weibull	£x,xxx	x.xx	£3,607	£xx,xxx	x.xx	£17,422

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr, incremental; Gen gamma, generalised gamma; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B7. Priority Question: The base case analysis uses HR to model differential OS post-CRc. These HR are informed by a matching adjusted indirect comparison (MAIC) of OS from the time of randomisation using IPD from the patients aged 60 or under in the QuANTUM-First trial and aggregate data from Rücker et al publication of the RATIFY trial.(19) This dcatch iffers fundamentally from the modelled outcome which is OS in patients who are in CRc and who have not received HSCT.

a. **Please justify the approach to modelling OS following CRc referring to the clinical plausibility of the modelled assumptions**

b. **The KM data (CS, Figure 28) from the QuANTUM-FIRST trial indicates that OS following CRc is inferior in the quizartinib arm compared to the SC arm. This contrasts with the economic model where the opposite is true. Please validate the modelled assumptions with reference to the observed data from QuANTUM-FIRST and explain this apparent contradiction.**

B7a Response: Based on the model structure inputs of survival after CRc are required for all regimens. However, the survival after CRc was not available in the RATIFY trial. Consequently, the OS (i.e. survival from randomisation) was utilised in the MAIC. Therefore, HR from randomisation was employed in the model as a proxy for HR from CRc, which was applied to the reference curve (i.e. survival after CRc for the

quizartinib arm), to ascertain the efficacy for midostaurin and SC. The underlying assumption is that the relative treatment effect in survival of midostaurin (versus quizartinib) was the same from randomisation and from CRc. Given the lack of data to estimate the relative treatment effect for survival after CRc, this is the best available measure of relative treatment effect between quizartinib and midostaurin. To understand the validity of the assumption, we evaluated post hoc the treatment effect between placebo and quizartinib on survival from randomisation (i.e. OS) and survival from CRc (i.e. endpoint used in the model). Trial data shows that the quizartinib treatment effect (vs placebo) is higher when looking at survival after CRc (HR = x.xxx) (39), comparing with survival from randomisation (HR = 0.780) (7). Based on this finding, it was deemed reasonable to assume the same treatment effect between quizartinib and midostaurin for survival from CRc and randomisation.

To test the sensitivity of the model outcomes to the assumed survival benefit of quizartinib over midostaurin, a scenario analysis that assumes the same death from CRc for both treatments was conducted (i.e. death from CRc HR=1). The results showed that the ICER of quizartinib vs. midostaurin (£3,271/QALY vs. £3,459/QALY gained) improved compared with revised base case (Table 35). Hence, the underlying assumption that the relative treatment effect in survival of midostaurin (versus quizartinib) was the same from randomisation and from CRc is not expected to have a significant impact on the cost-effectiveness of quizartinib.

Table 35. Scenario analysis supporting B7a

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,271
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,364

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B7b Response: A crossover was noted in the indicated curve (copied below, Figure 52). The KM curve for the SC arm remained flat from around month 11. The curves only crossed over around month 39, and this occurred when the numbers at risk were very low, which indicates a high uncertainty (Figure 52). Additionally, relapse was

censored in this analysis, thus any extended survival associated with extended time to relapse is not shown in this analysis.

Figure 52. KM curves for death from CRc, censored at the start date of all HSCT and relapse

Abbreviations: CRc, composite complete remission; KM, Kaplan Meier.

In the CS base case, the efficacy of SC arm was modelling by applying the HR generated from MAIC (HR = 0.65, 95%CI: 0.42, 1.00) to the quizartinib reference arm based on the QuANTUM-First trial data. Therefore, the KM curve was not directly used in the model in the base case. In addition, the quizartinib curve drops below the placebo curve (Figure 52) at approximately 39 months. However, cure modelling has been incorporated from three years. Thus, the crossover was not relevant to the economic evaluation under this assumption even if using KM curve.

To test the uncertainty, a scenario analysis was conducted using QuANTUM-First trial-based data to model the SC arm, and the KM curve + survival model was used to incorporate the KM data into the analysis. The results are presented in Table 36. This resulted in a slight increase in the ICER vs midostaurin (company revised base case: £3,459/QALY gained vs new scenario analysis ICER: £3,589/QALY gained) and in the ICER vs SC (£17,364/QALY gained vs £17,831/QALY gained).

Table 36. Scenario analysis supporting B7b

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,589
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,831

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

B8. Priority Question: The model uses time-invariant transition probabilities to model relapse following HSCT while simultaneously using time-varying transition probabilities to model OS following HSCT.

a. **Please justify this inconsistency.**

b. **Please provide scenario analysis using time-varying transition probabilities to model relapse following HSCT.**

B8a Response: Very few patients who received protocol-specified HSCT after achieving CRc subsequently relapsed (x=xx in the quizartinib arm and x=xx in the placebo arm) in the QuANTUM-First ITT analysis set (39). Due to this immaturity of the data, the time-varying survival for post-HSCT 1L relapse was too uncertain to be informative. Therefore, time-invariant inputs sourced from the adjusted QuANTUM-First population were used for the quizartinib and SC arms in the model to inform the transition from HSCT 1L to post-HSCT 1L relapse. It was assumed that the midostaurin treatment effect would be the same as SC since midostaurin maintenance is not licensed or NICE recommended post-HSCT.

B8b Response: A scenario analyses was conducted using time varying TPs for relapse following HSCT, based on the relapse from protocol-specified HSCT 1L KM data presented in Figure 53.

Figure 53. KM curve for relapse following HSCT

Abbreviations: CRc, composite complete remission; KM, Kaplan-Meier; TP, transition probability.

The overlay of the KM data and parametric extrapolations are presented in Figure 54 and Figure 55 for quizartinib and SC arm, respectively.

Abbreviations: CRc, composite complete remission.

Figure 54. Independent models for relapse from HSCT in the quizartinib arm (10 years)

Abbreviations: CRc, composite complete remission.

Figure 55. Independent models for relapse from HSCT in the SC arm (10 years)

Abbreviations: CRc, composite complete remission; SC, standard chemotherapy.

The best fitting curves were selected based on AIC and BIC scores, presented in Table 37.

Table 37. AIC and BIC scores for independent models of relapse from HSCT

Distribution	Quizartinib		SC	
	AIC	BIC	AIC	BIC
Generalized gamma	201.2	207.9	278.5	284.5
Gompertz	204.0	208.5	282.8	286.8
Log-normal	210.3	214.8	288.4	292.4
Log-logistic	212.2	216.7	290.9	294.9
Weibull	212.8	217.3	292.8	296.8
Gamma	213.2	217.7	294.0	298.0
Exponential	214.7	216.9	299.0	301.0

Abbreviations: AIC; akaike information criterion; BIC; bayesian information criterion; CRc, complete composite remission; SC, standard chemotherapy.

Generalised gamma was the model with the lowest AIC and BIC for both treatment arms, therefore it was selected for the analyses.

The results of this scenario analysis are presented in Table 38. Using time varying TPs for relapse after HSCT resulted in slightly lower incremental costs and higher incremental QALYs for quizartinib vs SC and midostaurin. Consequently, the ICERs for both comparisons are lower compared with the revised base case.

Table 38. Scenario analysis supporting B8b

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£2,940
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£16,777

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B9. Priority Question: Please utilise the analysis requested in question A9c to conduct a scenario analysis exploring the cost-effectiveness of treatment sequences that include post-HSCT maintenance therapy with sorafenib.

B9 Response: As described in the responses to question A9, the company intends to conduct an ITC to compare quizartinib with post-HSCT maintenance therapy with sorafenib, subject to completion of the feasibility analyses. Further responses to this question will be submitted by the 17th of May as agreed with NICE/EAG.

B10. Priority Question: Please utilise the analysis requested in question A17 to conduct a scenario analysis employing the unanchored matching adjusted indirect comparison with data derived from the AMLSG 16-10 trial.

B10 Response: the company has not completed the analysis requested in question A17 for the reasons outlined in the corresponding response section. Consequently, this scenario analysis cannot be completed.

Measurement and valuation of health effects

B11. Priority Question: EQ-5D data was collected in the QuANTUM-First trial for exploratory objectives for PRO endpoints, including assessment of changes to scores over time for both treatment arms in the induction, consolidation, and continuation phases. The health state utilities applied in the model rely on published values and do not incorporate the EQ-5D data from the trial. This presents an inconsistency with the NICE reference case in which the EQ-5D is the preferred measure of HRQoL in adults.

a. **Please provide further rationale for the exclusion of HRQoL values from the trial.**

B11a response: In the QuANTUM-First trial, HRQoL data was collected as an exploratory endpoint to assess the impact of quizartinib on PROs. However, the study was not designed to formally compare the treatment impact of quizartinib on patient reported outcome (PRO) measures with that of a placebo when combined with standard chemotherapy.

The design of the QuANTUM-First trial did not include the collection of PRO data during long-term follow-up, (i.e. after discontinuation) (40). Some PRO data was indeed collected immediately after relapse. However, clinician feedback suggests that the impact of relapse on the PRO is not immediately apparent post-relapse. As a result, the utility for refractory and relapse was not available from the QuANTUM-First trial due to the absence of PRO data collection during the long-term follow-up period.

Given the exploratory nature of the PRO analyses in QuANTUM-First, utility values used in the CS base case were sourced from the literature in line with TA523 (26).

Additionally, a scenario analysis using on-treatment utilities (i.e. for induction, consolidation, maintenance, and HSCT) collected from the QuANTUM-First is presented. The inputs used in this scenario and the results are shown below in the response for B11b.

b. Please provide a scenario analysis utilising the values generated from the trial; the EAG recognises it may be necessary to supplement this data with values from published studies

B11b response: A scenario analysis utilising the utility values generated from the QuANTUM-First trial was conducted based on the company revised base case. The summary of utility inputs used in the base case and scenario analysis supporting B11b is summarised in Table 39.

After applying the utility values collected from the QuANTUM-First trial, the QALYs increased for all three treatment strategies, resulting in very small variations on ICERs compared to the company revised base case (midostaurin: £3,431/QALY gained vs £3,459/QALY gained; SC: £17,176/QALY gained vs £17,364/QALY gained; detailed in Table 40). The results show that the model is not sensitive to the utility inputs.

Table 39. Summary of utility values for cost-effectiveness analysis used in the CS base case and scenario analysis supporting B11b

	CS base case		Scenario analysis supporting B11b	
Utility state	**Utility values**	**Reference**	**Utility values**	**Reference**
Induction	0.648	Uyl-de Groot et al. 1998 (41) in Tremblay et al. 2018 (42) and TA523 (26)	[redacted]	DS DOF. T_4_1_12 UK index score (Hernández Alava) - Descriptive summary of utility values by health state DCO 13-Aug-2021 - PRO Intent to Treat Analysis Set – patient-level.
Consolidation	0.710	Batty et al. 2014 (43) in Tremblay et al. 2018 (42) and TA523 (26)	[redacted]	DS DOF. T_4_1_12 UK index score (Hernández Alava) - Descriptive summary of utility values by health state DCO 13-Aug-2021 - PRO Intent to Treat Analysis Set – patient-level.
Maintenance	0.810	Batty et al. 2014 (43) in Tremblay et al. 2018 (42) and TA523 (26)	[redacted]	DS DOF. T_4_1_12 UK index score (Hernández Alava) - Descriptive summary of utility values by health state DCO 13-Aug-2021 - PRO Intent to Treat Analysis Set – patient-level.
HSCT 1L	0.750	Source for Algorithm: Crott (2010) (44); Source of QLQC30 data: Grulke (2012) (45) - Calculation in Midostaurin STA (46) - Average of following utility values from TA523: SCT treatment (0.613), SCT recovery (0.810), and Post-SCT recovery (0.826)	[redacted]	DS DOF. T_4_1_12 UK index score (Hernández Alava) - Descriptive summary of utility values by health state DCO 13-Aug-2021 - PRO Intent to Treat Analysis Set – patient-level.
HSCT 2L	0.552	Assumption: 90% of the utility for the 1L health state used in the TA523 (0.613) (26)	[redacted]	Assumption: 90% of the utility for the 1L health state (0.825).

Abbreviations: CS, company submission; DOF, Data on file; DS, Daiichi Sankyo; HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; PRO, patient reported outcome; QLQC30, Core Quality of Life questionnaire; Relaspe1, first relapse; Relapse 2, second relapse; STA, single technology appraisal; 1L, first line treatment; 2L, second line treatment.
Note: The utilities used are in line with those from TA523 (26)

Table 40. Scenario analysis supporting B11b

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,431
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,176

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

Resource Use

B12. Priority Question: The EAG is concerned that the economic model incorrectly estimates time on treatment. Currently, the economic model uses mean time on treatment data observed in QuANTUM-FIRST to model time on treatment and this is linked to state occupancy on the Cost-calcs sheet to estimate total drug acquisition costs. The EAG considers that this approach is very likely incorrect. Firstly, this approach does not account for the fact that observed time on treatment will already account for state occupancy. Secondly, it does not appropriately account for the fact that dosing is different in the induction/consolidation vs. maintenance phase.

a. **Please validate the current approach to modelling time on treatment ensuring that it reflects time on treatment observed in the QuANTUM-First trial.**

b. **For the consolidation phase, please provide KM data for time on treatment censored for relapse and HSCT. If this is not possible, please provide data on the proportion of patients discontinuing treatment for reasons other than relapse or HSCT.**

c. **For patients who do not proceed to HSCT, please provide KM data for time on treatment censored for relapse and HSCT. If this is not possible, please provide data on the proportion of patients discontinuing treatment for reasons other than relapse or HSCT.**

d. **For patients who proceed to HSCT, please provide KM data for time on treatment censored for relapse and HSCT. If this is not possible please provide data on the proportion of patients discontinuing treatment for reasons other than relapse or HSCT.**

B12a Response: Table 34 of CS Document B presents the mean quizartinib treatment duration of xx.xx weeks, using the 13 August 2021 DCO. This is revised to xx.xx weeks using the later 16 June 2023 cut-off (Safety Analysis Set). No patient was ongoing with the study drug in this update. The duration of xx.xx weeks compares well with the mean modelled quizartinib treatment duration of xx.xx weeks used in the revised base

case. The modelled estimate is calculated as described in the CS Document B B.3.5.1.1, and as described in the question, it is the result of health state occupancy time capped according to the estimated mean time on treatment data observed in QuANTUM-First for the maintenance treatment phase. The use of mean time on treatment as the duration cap was validated with expert clinical input. In an extreme scenario analysis using an alternative and extended treatment duration cap of 42 cycles (6+36) for quizartinib, representing the maximum permitted treatment duration, the modelled mean time on treatment rose to xx.xx weeks, considerably higher than the empirical measurement. Although we consider this approach overestimates treatment costs, we conducted an extreme exploratory scenario to evaluate the impact on the CEM outcomes. The results are presented in Table 41.

Table 41. Scenario analysis supporting B12a

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£20,763
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£31,024

Abbreviations: LYG, life years gained, QALY, quality adjusted life year; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B12b Response: A KM curve for time on treatment (starting at the consolidation phase) censored for relapse and HSCT is presented in Figure 56.

The company has several concerns with this EAG request as we consider the requested KM data is not informative to estimate treatment costs for quizartinib considering the model structure. Patients transition to CR1 after induction and start receiving consolidation therapy. In the trial, patients received HSTC between 1.3 and 12.3 months after start of consolidation therapy. However, in the CEM, a simplifying assumption was made so that all patients receive HSCT in the same cycle. Therefore, it is not possible to estimate treatment costs for the consolidation phase alone using these KM curves.

In addition, the KM curve does not provide information regarding the actual time on treatment for quizartinib as the censoring rules requested by the EAG result in exclusion of time on treatment data for most patients as the majority stops treatment

due to relapse. The maximum duration of treatment should therefore be 42 cycles (2 induction + 4 consolidation + 36 maintenance) or ~38.6 months. Therefore, the time on treatment curve should drop to 0 after this time. However, due to the censoring for relapse, these KM curves do not capture this.

Figure 56. KM curve for time on treatment censored for relapse and HSCT

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; KM, Kaplan-Meier.

B12c Response: A KM curve for time on treatment (from start of the consolidation phase) those that did not proceed to HSCT censored for relapse and HSCT is presented in Figure 57.

As with the KM curve provided in the previous question, the company considers that this is not informative to estimate treatment costs. In the CEM, patients that did not proceed to HSCT remain in the CR1 and CR2 health states and all patients that receive HSCT transition to the HSCT health state in cycle 5. However, this was a simplifying assumption to enable survival post HSCT to be informed by QUANTUM-First data. In the trial, patients received HSCT over a period of 12 months. The KM curve below censors HSCT patients at the date of the procedure therefore, it is not aligned with the CEM structure. From cycle 5 onwards, all patients remaining in the CR1 health state do not proceed to HSCT whereas the KM curve also includes time on treatment from patients who proceed to HSCT after that time point.

Figure 57. KM curve for time on treatment for those that did not proceed to HSCT censored for relapse and HSCT

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; KM, Kaplan-Meier.

B12d Response: A KM curve for time on treatment (from start of the consolidation phase) for those that proceeded to HSCT censored for relapse and HSCT Figure 58.

The company considers that the KM curve requested does not provide information regarding the time on treatment for patients who proceed to HSCT, as patients are censored at the date of the HSCT procedure. Therefore, their time on treatment is not captured in these analyses. This is evident from the KM curves shown below (no information after ~8 months for quizartinib).

The company considers that a time on treatment analyses starting at the date of treatment initiation after HSCT until discontinuation for any reason would be more informative to inform treatment duration of quizartinib for these patients.

Figure 58. KM curve for time on treatment for those that proceeded to HSCT censored for relapse and HSCT

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; KM, Kaplan-Meier.

B13. Priority Question: The economic model assumes that [redacted] of patients who receive HSCT will proceed to receive maintenance treatment with quizartinib. It is currently unclear how this figure has been derived.

a. **Please clarify how this figure was estimated, supported by evidence as appropriate.**

b. **Please provide data on the proportion of patients who received quizartinib or other maintenance treatments following HSCT.**

B13a Response: As presented in the Table 42, there were xxx patients who underwent HSCT after CRc in the quizartinib arm in the QuANTUM-First trial. Out of these xxx patients, xx had at least one study treatment administration after HSCT. This percentage of xx.x% was calculated by dividing xx by xxx.

Table 42. Number of patients with HSCT after CRc and at least one study treatment administration after HSCT – ITT Analysis Set

	Quizartinib (N=268)	Placebo (N=271)
Number of patients with HSCT after CRc	xxx	xx

	Quizartinib (N=268)	Placebo (N=271)
Number of patients with HSCT after CRc and at least one study treatment administration after HSCT	xx	xx

Abbreviations: CRc, composite complete remission; HSCT, allogeneic hematopoietic stem cell transplantation; ITT, intent-to-treat.
Source: Daiichi Sankyo internal analysis, 2023 (47)

B13b Response: As described in the response to question B13a, xx.x% of patients who received HSCT proceeded to receive maintenance treatment with quizartinib. This data was collected from the QuANTUM-First trial. Based on the trial design, patients did not proceed to receive any other maintenance treatment if they did not receive quizartinib.

B14. In the scenario analysis modelling post HSCT maintenance treatment with sorafenib, it is assumed that 70% will receive quizartinib. Please justify the difference between the [redacted] figure applied to quizartinib maintenance treatment and the 70% figure applied in the sorafenib maintenance scenarios.

B14 Response: In the base case, xx.x% of patients was assumed to receive quizartinib maintenance treatment post-HSCT. This is based on data from the QuANTUM-First trial (as explained in response B13a).

In the CS submitted scenario analysis, which models post-HSCT maintenance treatment with sorafenib, it was assumed that 70% of patients would receive sorafenib. This assumption was based on KOL feedback, which indicated that 70% of patients are eligible for sorafenib maintenance treatment post-HSCT.

An additional scenario analysis has now been run based on the company revised base case, which adjusts the proportion of patients that receive sorafenib maintenance treatment post-HSCT to xx.x%. Same as described in the CS document B 3.9.3, when applying this scenario, it was assumed that sorafenib survival post-HSCT was equivalent to the quizartinib arm of the QuANTUM-First trial and included the costs of sorafenib.

As presented in Table 43, the total costs and total QALYs both slightly increased in the midostaurin arm. However, this resulted in a limited impact on the ICERs vs midostaurin (£3,459/QALY gained vs £3,347/QALY gained). The results in the SC arm remain the same as the base case.

Table 43. Scenario analysis supporting B14

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,347
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,364

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B15. The economic model assumes that a differing proportion of patients will receive gilteritinib in the refractory and relapse setting (Table 68 of the CS) while also assuming equal efficacy across all treatment arms. This means that the model accounts for the additional costs of gilteritinib without modelling associated benefits.

a. **Please provide a clinical rationale for assuming differential treatment in the refractory and relapse setting and justify the assumption of equal efficacy.**

b. **Please provide a scenario analysis in which the transition probabilities applied in the refractory, relapse 1 and post-HSCT health states are linked to the subsequent treatments received.**

c. **Clinical advice received by the EAG suggests that the vast majority (90%) of patients in the NHS will receive gilteritinib regardless of first-line treatment received. Please justify the modelled assumptions (CS, Table 68) and provide a scenario analysis assuming 90% of patients will receive gilteritinib across all treatment arms.**

B15a Response: The distribution of treatments was not equal between arms but depended on the 1L treatment regimen received as outlined in Table 44. This distribution was from clinical expert advice (32) and was on the basis that a patient would be more likely to receive a 2nd generation FLT3 inhibitors (FLT3i) (i.e. gilteritinib) at 2L if a 2nd generation FLT3i (e.g. quizartinib) wasn't already received at 1L. As a result, patients that receive the midostaurin regimen (midostaurin being a 1st generation FLT3i) would be more likely to receive gilteritinib in 2L than those that receive the quizartinib regimen.

Table 44. Treatment distribution for the subsequent treatment regimens in the CEM

2L regimen	1L quiz	1L SC	1L mido
FLAG-Ida	60%	50%	40%
Gilteritinib	40%	50%	60%

Abbreviations: CEM, cost-effectiveness model; FLAG-Ida, fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; G-CSF, granulocyte colony stimulating factor; IV, intravenous; 1L, first-line treatment; quiz, quizartinib; mido, midostaurin; RDI, relative dose intensity; SC, standard chemotherapy.

TPs from relapse1, CR2 and the refractory health state were derived from pooled data from the ADMIRAL trial (i.e. including patients who received gilteritinib and FLAG-Ida). The assumption of equal efficacy aims to reduce the over-complexity in 2L in the model because quizartinib and its main comparators are indicated in the 1L. To explore the uncertainty around this assumption, two scenario analyses have been conducted as suggested by the EAG, see response in B15b and B15c.

B15b Response: A scenario analysis was conducted to allow the transition probabilities that sourced from the ADMIRAL trial and applied in the refractory, relapse 1 and CRs to link to the percentage of FLAG-Ida and gilteritinib received. The inputs used in this scenario have been summarised in

Table 46. The cumulative relapse rates in the SC arm could not be calculated in the ADMIRAL trial. Thus, the transition from CR2 to Relapse 2 was based solely on the data from the gilteritinib arm, and it could not be pooled or reweighted. Consequently, this input remains the same across all analyses.

Table 45. Transition probabilities inputs from Refractory, Relapse1 and CR2 supporting questions B15

Transition from[a]:	Transition to:	Tp %, in CS base case	Tp %, in scenario supporting B15b	Tp %, in scenario supporting B15c
Refractory	CR2	14.3	14.8	14.2
	Death	5.2	6.5	4.0
Relapse 1	CR2	30.0	24.8	35.4
CR2	Relapse 2[a]	2.2	2.2	2.2
	HSCT 2L	12.5	13.5	12
	Death	2.8	2.3	3.4
Reference		Perl, 2019 (30), pooled data from the gilteritinib arm and salvage chemotherapy arm	Perl, 2019 (30), reweighted based on the percentage use of gilteritinib and salvage chemotherapy in CS base case (Table 44)	Perl, 2019 (30), reweighted based on assuming 90% usage of gilteritinib

Abbreviations: CR, complete remission; CRh, complete remission with partial hematologic recovery; CR1, first CR; CR2, second CR; HSCT, haematopoietic stem cell transplantation; Relapse1, first relapse; Relapse2, second relapse; SC, standard chemotherapy; 1L, first-line treatment; 2L, second-line treatment.
Reference: Perl, 2019 (30)
Notes: a. A meaningful assessment of cumulative relapse rates in the SC arm could not be performed because bone marrow samples were only collected up to the end of treatment, and nearly all patients in the SC arm had

discontinued treatment after ≤2 treatment cycles. Thus, this input was not be able to be pooled or reweighted in the CS base case and new scenario analysis. Consequently, this input remain the same across all analyses.

After linking the percentage usage of subsequent treatment to the transition probability, compared with the company revised base case, the ICER was slightly lower when comparing quizartinib vs midostaurin (£3,549/QALY gained vs £3,432/QALY gained) and slightly higher when comparing quizartinib vs SC (£17,364/QALY gained vs £17,384/QALY gained). The results of this scenario analysis are presented in Table 46.

Table 46. Scenario analysis supporting B15b

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,432
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,384

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B15c Response: A scenario analysis has been conducted assuming 90% of patients will receive gilteritinib across all treatment arms. This scenario was conducted with TPs linked to the distribution of subsequent treatments.

As presented in Table 47, the total costs increased in all three arms due to a higher percentage use of gilteritinib. This resulted in an improvement in both the ICER vs midostaurin (£3,549/QALY gained vs £3,387/QALY gained) and the ICER vs SC (£17,364/QALY gained vs £15,217/QALY gained).

After an alternative way of modelling the efficacy of subsequent line treatment was explored in a scenario, for question B15, the results indicate that there is a minor impact on the ICER, which demonstrates limited uncertainty around this topic.

Table 47. Scenario analysis supporting B15c

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,387
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£15,217

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

Model validation

B16. Priority Question: The proportion of patients proceeding to protocol-specified HSCT appears to have been estimated incorrectly. The estimated proportion of patients proceeding to HSCT appears to have been estimated using the whole population as the denominator (n=539) (CS, Table 48). This is inconsistent with how this value is applied in the model where this is applied as condition probability in those who have achieved CRc. The denominator should therefore be the number achieving CRc (n=368). This would imply that the pooled rate of patients proceeding to protocol-specified HSCT is [redacted], not [redacted]. Please confirm this error and provide revised results for the economic model.

B16 Response: The company agrees that there was an error in the model. The revised base case corrects this error. Please find more details of the revised base case in section Revised Company Base Case.

To test the impact of this error in isolation, a scenario analysis was conducted where this error was revised in the original company-submitted base case. The results for this scenario analysis are provided in Table 48.

Because this pooled rate of protocol-specified HSCT after achieving CRc was applied to all three interventions in the model, the QALYs for all three arms increased after correcting this error, as more patients underwent the HSCT. The total costs for the quizartinib regimen and the midostaurin regimen decreased, but they increased for the SC regimen. The scenario still resulted in quizartinib being cost-effective compared with midostaurin and SC regimen.

Table 48. Scenario analysis supporting B16 (not including correction for 1L HSCT costs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	[redacted]	[redacted]	[redacted]	-	-	-	-
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,953

SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£16,150

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B17. Priority Question: Please check cell F250 on Sheet 'Dosing Schedule'. The EAG believes this value should be [redacted], not [redacted]. If this is an error, please confirm and provide revised results for the economic model.

B17 Response: The company agree that there was an error in the model. A revised base case is provided to correct this error. Please find more details of the revised base case in section Revised Company Base Case.

To test the impact of this error in isolation, a scenario analysis was conducted where this error was revised in the original company-submitted base case. The results for this scenario analysis are provided in Table 49. After correcting this error, the total costs of the quizartinib regimen slightly increased. The results show that quizartinib is still dominant compared to midostaurin, and the ICER compared with SC slightly increased compared with original company-submitted base case (£15,851/QALY gained vs £15,866/QALY).

Table 49. Scenario analysis supporting B17 (not including correction for 1L HSCT costs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	-£x,xxx	x.xx	x.xx	Dominant
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£15,866

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results use the quizartinib PAS price.

B18. Priority Question: The model uses trial data to inform time on treatment and sensitivity analysis, drawing from the Daiichi Sankyo internal analysis, 2023. The CS also references the Daiichi Sankyo Inc. Post-hoc analysis, 2024, for treatment duration and support for certain assumptions. Please provide information describing how these inputs were derived, including the appropriate references.

B18 Response: Table 50 contains the results of the internal analysis which was used to inform time on treatment.

Table 50. Treatment exposure - Duration of treatment during maintenance by HSCT status - DCO 13-Aug-2023 - Safety analysis set

		Quizartinib (N=265)	Placebo (N=268)
Treatment Duration of Quizartinib during maintenance (weeks)[a]			
In all patients	N	xxx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min; Max	x.x, xxx.x	x.x, xxx.x
	Missing	x	x
In patients with protocol-specified HSCT	N	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min; Max	x.x, xxx.x	x.x, xxx.x
	Missing	x	x
In patients without protocol-specified HSCT	N	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min; Max	x.x, xxx.x	x.x, xxx.x
	Missing	x	x

Abbreviations: DCO, data cut off; HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
Notes: Only protocol-specified HSCT are considered in this table. Treatment Duration (weeks) for each phase = (last dose date - first dose date + 1 within each phase)/7. a. If there are some patients with non-protocol specified HSCT before maintenance and who entered the maintenance phase, these patients are excluded from the table.

The data is converted from duration in weeks to duration in cycles (i.e. dividing by 4) for use in the model (Table 51).

Table 51. Treatment exposure - Duration of treatment during maintenance by HSCT status

	Data extracted from Table 50	Model input
	Quizartinib treatment duration (weeks)	Quizartinib treatment duration (cycles i.e. divided by 4)
In patients with protocol-specified HSCT	xx.x	xx.xx
In patients without protocol-specified HSCT	xx.x	xx.xx

Abbreviations: transplantation. These results use the quizartinib PAS price.

Section C: Textual clarification and additional points

Systematic review

C1. Please clarify the number of publications (and trials) that met the inclusion criteria of the SLR. Document B states that the SLR identified 18 publications (describing 11 clinical trials), whereas Appendix D states that 36 publications (24 studies) met inclusion criteria.

C1 Response: The SLR, which is described in Appendix D, included newly diagnosed AML patients with a *FLT3* mutation. In document B, however, only studies presenting results on patients with a *FLT3-ITD* mutation were described as this aligned with the scope of the submission.

Upon re-examination of the values, a transcription error was identified in Document B. In total 12 publications describing 6 clinical trials aligned with the scope.

C2. Please justify the exclusion of HRQoL in the list of outcomes in the SLR (Table 1, Appendix D), since it was an outcome of interest in the NICE scope?

C2 Response: A separate SLR was conducted to identify HRQoL evidence. Please find more detail in Appendix H.

Literature searching

C3. Some of the SLR searches do not have search strategies reported in the appendices. Please provide search strategies for all conferences searches, all trial registry searches and for searches of the International Network of Agencies for Health Technology Assessment (INAHTA) database for the following:

- **Appendix D – Clinical effectiveness SLR**
- **Appendix G – Cost-effectiveness SLR**
- **Appendix H – Health related quality of life SLR (Please also provide a search strategy for the School of Health and Related Research (ScHARR) Health Utilities Database)**
- **Appendix I – Cost and healthcare resources use SLR**

C3 Response: The key words used for the hand search of conference proceedings, trial registries and HTA databases are outlined in Table 52.

Table 52. Search strategy for hand search

Hand search	Description	Search Conducted (Date)	Key words
Conference proceedings	European Hematology Association	18-May-23	FLT3, acute myeloid leukemia
	American Society of Clinical Oncology	18-May-23	acute myeloid leukemia, flt3
			acute myeloid leukaemia, flt3
	European Society for Medical Oncology	18-May-23	acute myeloid leukemia, flt3
			acute myeloid leukaemia, flt3
	International Society for Pharmacoeconomics and Outcomes Research	18-May-23	acute myeloid leukemia, flt3
			acute myeloid leukaemia, flt3
	European LeukemiaNet	18-May-23	N/A
	American Society of Hematology	18-May-23	acute myeloid leukemia, flt3
			acute myeloid leukaemia, flt3
Trial Registries	Clinical trials.gov	3-Jul-23	acute myeloid leukemia, flt3, AML, fms-like tyrosine kinase 3
	International Clinical Trials Registry Platform (ICTRP)	18-May-23	AML or acute myeloid leukemia or acute myeloid leukaemia cd135 or flt3 or flt 3 or fms like tyrosine kinase 3
	EU Registry	18-May-23	acute myeloid leukemia, flt3
	Clinical Data search portal EMA	18-May-23	acute myeloid leukemia, flt3
HTA database	National Institute for Health and Care Excellence Technical Assessments	11-Aug-23	AML
	International HTA database	11-Aug-23	aml flt 3
	School of Health and Related Research	11-Aug-23	AML

C4. Please provide details of any study design search filters used in the search strategies reported in the following:

- **Appendix D – Clinical effectiveness SLR**
- **Appendix G – Cost-effectiveness SLR**
- **Appendix H – Health related quality of life SLR**
- **Appendix I – Cost and healthcare resources use SLR**

For each search filter please provide a reference.

C4 Response:

Clinical SLR – Appendix D

For the search in Embase®, animal studies, case reports, and editorials were filtered out (see Table 2 of Appendix D).

For the search in Ovid MEDLINE®, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 3 Appendix D).

For the search in EBM Reviews, no study design filters were used (see Table 4 Appendix D).

Cost-effectiveness SLR – Appendix G

For the search in Embase®, animal studies, case reports editorials, and notes were filtered out (see Table 2 of Appendix G).

For the search in Ovid MEDLINE®, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 3 Appendix G).

For the search in EBM Reviews, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 4 Appendix G).

For the search in EconLit, no study design filters were used (see Table 5 Appendix G).

HRQoL SLR – Appendix H

For the search in Embase®, animal studies, case reports, and editorials were filtered out (see Table 2 of Appendix H).

For the search in Ovid MEDLINE®, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 3 Appendix H).

For the search in EBM Reviews, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 4 Appendix H).

Cost and healthcare resource use SLR – Appendix I

For the search in Embase®, animal studies, case reports editorials, and notes were filtered out (see Table 2 of Appendix I).

For the search in Ovid MEDLINE®, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 3 Appendix I).

For the search in EBM Reviews, animal studies/not human studies, editorials, historical articles, and case reports were filtered out (see Table 4 Appendix I).

For the search in EconLit, no study design filters were used (see Table 5 Appendix I).

Other textual clarification

C5. Figure 7.1 and Table 7.2 of the CSR report that 225 subjects in the quizartinib arm entered the Long-term Follow-up Phase, but this is reported as 255 in Figure 2, Appendix D. Please confirm what the correct figure is.

C5 Response: The value presented in the CSR is correct; 225 subjects in the quizartinib arm entered the long-term follow-up phase.

C6. Please clarify whether the number of patients receiving protocol-specified HSCT is commercial-in-confidence data; it is marked CIC in Table 20 of Document B, but not in Figure 2, Appendix D.

C6 Response: The number of patients receiving protocol-specified HSCT is not commercial-in-confidence data.

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Appendix 1. Supporting question A15

```
################## 1.0 Introduction--------------------------------------
---------

# Multi-level Network Meta-Regression

library(multinma)
library(dplyr)
library(tidyr)
library(ggplot2)
library(readxl)
library(OHplot)
library(shinystan)
library(tidyverse)
library(haven)
library(MMAsurvival)
library(splines2)
library(loo)
#library(sandwich)
#library(epitools)

# Use multiprocessing
options(mc.cores = parallel::detectCores())

# Trial Names =
## QuANTUM-First - IPD, Quizartinib vs Placebo in AML with FLT-3-ITD
positive patients
## RATIFY - Based on Rucker et al, Midostaurin vs Placebo in AML with FLT3-
ITD positive patients

## Complete Remission ===
outcome <- "CR"
cr_source <- "Number at risk" # TODO: Select any one of: "Multivariate
regression" OR "Number at risk"
cr_completecases <- "Complete Cases" # TODO: Select any one of:  "Complete
Cases" OR "Imputation"

if(cr_source == "Number at risk") {
  ratify_midostaurin <- 230
  ratify_placebo <- 222
  ratify_midostaurin_cr <- 165
  ratify_placebo_cr <- 147

  ratify_cr_or <- ratify_midostaurin_cr *
    (ratify_placebo - ratify_placebo_cr) /
    (ratify_placebo_cr *
       (ratify_midostaurin - ratify_midostaurin_cr))

  ratify_cr_or_log <- log(ratify_cr_or)

  ratify_cr_var <- (1/ratify_midostaurin_cr) +
    (1/(ratify_placebo - ratify_placebo_cr)) +
    (1/ratify_placebo_cr) +
    (1/(ratify_midostaurin - ratify_midostaurin_cr))

  ratify_cr_se <- sqrt(ratify_cr_var)

  ratify_cr_or_lci <- exp(ratify_cr_or_log - qnorm(0.975) * ratify_cr_se)
  ratify_cr_or_uci <- exp(ratify_cr_or_log + qnorm(0.975) * ratify_cr_se)
}
```

```
if(cr_source == "Multivariate regression") {
  ratify_midostaurin <- 230
  ratify_placebo <- 222
  ratify_cr_or <- 1.25
  ratify_cr_or_log <- log(ratify_cr_or)
  ratify_cr_or_lci <- 0.79
  ratify_cr_or_uci <- 1.99
  ratify_cr_se <- (log(ratify_cr_or) - log(ratify_cr_or_lci))/qnorm(0.975)
  ratify_cr_var <- ratify_cr_se ^ 2
}

# 2.0 IPD data from Quantum First =================

## adsl: subject level dataset
## adrs: tumor response analysis dataset
## adtte: time to event data
adsl <- read_sas("adsl.sas7bdat") %>%
  select("AAGE", "ITTFL", "SEX", "RACE", "BLASTBL",
         "NEUTBL", "PLATBL", "FLT3CAT", "FLT3BL", "ANTHRTYP",
         "RISKSTAT", "USUBJID", "ECOGBL", "IVRSWBC", "WBCCNT",
         "WBCCOUNT", "NPM1MUT", "NPM1WILD")

adrs <- read_sas("adrs.sas7bdat") %>%
  select(USUBJID, TRTP, ADT2, AVAL, AVALC, CRDY, CRIDY)

adtte <- read_sas("adtte.sas7bdat") %>%
  select(treatment = "TRTPN", "AP01SDT", "USUBJID", "EVNTDESC",
         "AVAL", "ADT", "STARTDT", outcome = "PARAMCD",
         "RANDDT", "CNSR") %>%
  rename_all(tolower)


# 3.0 Prep TEM data from Q-First ==========================
tem <- adsl %>%
  filter(ITTFL == "Y") %>%
  mutate(male = if_else(SEX == "M", 1, 0),
         female = if_else(SEX == "F", 1, 0),
         npm1_positive = if_else(NPM1MUT == "Y", 1, 0),
         npm1_negative = if_else(NPM1WILD == "Y", 1, 0),
         ar_raw = (FLT3BL * 0.01) / (1 - (FLT3BL * 0.01)), # Convert VAF to
AR
         allelic_ratio_high = if_else(ar_raw > 0.7, 1, 0),
         allelic_ratio_low = if_else(ar_raw <= 0.7, 1, 0)) %>%
  select(USUBJID, AAGE, PLATBL, NEUTBL, male, female, npm1_positive,
npm1_negative, allelic_ratio_high, allelic_ratio_low) %>%
  group_by(USUBJID) %>%
  summarise(age = unique(AAGE),
            male = unique(male),
            female = unique(female),
            plc = unique(PLATBL),
            anc = unique(NEUTBL),
            npm1_positive = unique(npm1_positive),
            npm1_negative = unique(npm1_negative),
            allelic_ratio_high = unique(allelic_ratio_high),
            allelic_ratio_low = unique(allelic_ratio_low)) %>%
  ungroup() %>%
  rename_all(tolower)


cr <- adrs %>%
```

```
  mutate(cr_status = case_when(is.na(CRDY) ~ 0,
                               CRDY <= 120 ~ 1,
                               CRDY > 120 ~ 0)) %>%
  select(USUBJID, TRTP, cr_status) %>%
  distinct(USUBJID, .keep_all = TRUE) %>%
  rename_all(tolower) %>%
  left_join(tem, by = "usubjid") %>%
  #  left_join(weights_data) %>%
  # filter(age <= 60) %>%


  mutate(treatment = if_else(trtp == "Placebo", 0, 1),
         trtclass = case_when(treatment == 0 ~ "Placebo",

                              treatment == 1 ~ "TKI"))

cr$study<-"Quantum"
initial_r<-table(cr$cr_status, cr$treatment)
print(initial_r)
## In UK Analysis only 3 patients will be excluded

##### problem with missing data; conduct mice (multiple imputation for plc)
##https://bookdown.org/mwheymans/bookmi/multiple-imputation.html#multiple-
imputation-in-r
if(cr_completecases == "Imputation") {
  library(mice)
  library(foreign)
  data <-
cr[,c("plc","age","male","cr_status","trtp","anc","allelic_ratio_low",
"npm1_positive")] # Read in dataset an exclude ID variable
  data$cr_status = as.factor(data$cr_status)
  data$male = as.factor(data$male)
  data$allelic_ratio_low = as.factor(data$allelic_ratio_low)
  imp <- mice(data, m=5, maxit=20)

  imp$method
  #allelic_ratio_high are no missing values, in low there are - odd
  cr_new<-complete(imp, action = 1)
  cr_new$allelic_ratio_low = as.numeric(cr_new$allelic_ratio_low)-1

  cr<-
cbind(cr[,c("usubjid","trtp","cr_status","age","male","treatment","study","
trtclass","npm1_positive")],cr_new[,c("plc","anc","allelic_ratio_low")])
}


if(cr_completecases == "Complete Cases") {
  cc_arl<-complete.cases(cr[,"allelic_ratio_low"])
  cc_plc<-complete.cases(cr[,"plc"])
  cr <- filter(cr, cc_arl&cc_plc)  ## 4 observations dropped
  new_r<-table(cr$cr_status, cr$treatment)
  print(new_r)
}

# 4.0 RATIFY FLT3-ITD characteristics - Rucker et al
=======================

# ML-NMR Input for Aggregate Trial Data

## TEMs included for NICE Analysis: Age, Sex, NMP1 positive, Platelet count
```

```
crr_n<-c(ratify_midostaurin,ratify_placebo)
## Age
age<-c(47,48)
age_sd<-c((59-19)/4,(60-18)/4)
## Sex
male<-c((ratify_midostaurin - 116)/ratify_midostaurin,(ratify_placebo -
130)/ratify_placebo)
## FLT3 - High vs low allelic ratio
allelic_ratio_low<-c(171/ratify_midostaurin, 170/ratify_placebo)
## Platelet count
plc<-c(50.5,49.5)
plc_sd<-c((461-2)/4,(342-8)/4)
## nmc positive
nmc_pos <-  c((95/190),(108/168))
## Absolute neutrophil count (ANC)
anc<-c(2.2,2.3)
anc_sd<-c(55.9/4,55.9/4)

trtc<-c("Midostaurin","Placebo")
crr_r<- c(ratify_midostaurin_cr,ratify_placebo_cr)

study<-"RATIFY"
RAT.AgD<-data.frame(age, age_sd, male, allelic_ratio_low,
plc,plc_sd,anc,anc_sd, nmc_pos, trtc, crr_r, crr_n, study)
RAT.AgD<-RAT.AgD %>%
  mutate(
    trtclass = case_when(trtc == "Midostaurin" ~ "TKI",

                         trtc == "Placebo" ~ "Placebo"))


##################### 5.0 Creating the Network ----------------------------
net <- combine_network(
  set_ipd(cr,
          study = study,
          trt = trtp,
          r = cr_status,
          trt_class = trtclass ),
  set_agd_arm(RAT.AgD,
              study = study,
              trt = trtc,
              r = crr_r,
              n = crr_n,
              trt_class =trtclass)
)

net

# Plot the network figure using the following

net_plot <- plot(net, weight_nodes = TRUE, weight_edges = TRUE,
show_trt_class = TRUE) +
  ggplot2::theme(legend.position = "bottom", legend.box = "vertical")


##################### 6.0 Numerical Integration for ML-NMR ----------------
------------

# We now set up the numerical integration for the network.
# We need to choose marginal distributions for each of these covariates to
draw integration points from.
```

```
# Sex and NMP1 positive are binary covariate so these are given a Bernoulli
distribution
# We check the covariates age and platelet count for what distributions we
should give

dens_plot_age <- ggplot(cr, aes(age)) +
  geom_histogram(colour = "white", fill = OH_DuskySky) +
  OH_style() +
  theme(text = element_text(size=21.5))

dens_plot_plc <- ggplot(cr, aes(plc)) +
  geom_histogram(colour = "white", fill = OH_DuskySky) +
  OH_style() +
  theme(text = element_text(size=21.5))

# Gamma distribution looks suitable for age
# Gamma or normal look suitable for platelet count

# Given the skew of the data a gamma distribution seems reasonable to
assume

ipd_summary <- cr %>%
  summarise_at(vars(age, plc), list(mean = mean, sd = sd, min = min, max =
max)) %>%
  pivot_longer(age_mean:plc_max, names_sep = "_", names_to = c("covariate",
".value")) %>%
  # Assign distribution
  group_by(covariate) %>%
  mutate(dist = recode(covariate,
                       age = "dgamma",
                       plc = "dgamma")) %>%
  mutate(value = if_else(dist == "dgamma",
                         list(seq(from = min*0.8, to = max*1.2, length.out
= 101)),
                         list(seq(from = 0, to = max*1.2, length.out =
101)))) %>%
  unnest(cols = value) %>%
  mutate(dens = eval(call(first(dist), x = value, mean = first(mean), sd =
first(sd))))

# Plot histograms and assumed densities

(dist_plot <- cr %>%
    pivot_longer(c(age, plc), names_to = "covariate", values_to = "value")
%>%
    ggplot(aes(x = value)) +
    geom_histogram(aes(y = after_stat(density)),
                   binwidth = function(x) diff(range(x)) /
nclass.Sturges(x),
                   boundary = 0,
                   fill = OH_DuskySky,
                   colour = "white") +
    geom_line(aes(y = dens), data = ipd_summary,
              colour = OH_pink, linewidth = 0.5) +
    facet_wrap(~covariate, scales = "free") +
    OH_style() +
    theme(text = element_text(size=21.5)))

net_all <- add_integration(net,
                           age = distr(qgamma, mean = age, sd = age_sd),
                           male = distr(qbern, prob = male),
```

```
                            #allelic_ratio_low = distr(qbern, prob =
allelic_ratio_low),
                            plc = distr(qgamma, mean = plc, sd = plc_sd),
                            #anc = distr(qgamma, mean = anc, sd = anc_sd),
                            npm1_positive= distr(qbern, prob = nmc_pos),
                            n_int = 64
)

##################### 7.0 Fitting FE ML-NMR Models ----------------------
----

fit_FE <- nma(net_all,
              trt_effects = "fixed",
              link = "logit",
              likelihood = "bernoulli2",
              regression = ~(age + male + plc + npm1_positive)*.trt,
              class_interactions = "common",
              prior_intercept = normal(scale = 10),
              prior_trt = normal(scale = 10),
              prior_reg = normal(scale = 10),
              #iter = 50000,
              init_r = 0.1,
              int_thin = 1,
              QR = TRUE)

print(results_FE <- (fit_FE))
print(results_FE <- summary(fit_FE))
print(releff_FE <- relative_effects(fit_FE, all_contrasts = TRUE))

OR_FE <- releff_FE$summary %>% mutate(mean = round(exp(mean),4), sd =
round(exp(sd),4), `2.5%` = round(exp(`2.5%`),4),`25%` =
round(exp(`25%`),4), `50%` = round(exp(`50%`),5),`75%` =
round(exp(`75%`),5), `97.5%` = round(exp(`97.5%`),5))
OR_FE <- OR_FE %>% select(.study, .trtb, .trta, parameter, mean, `50%`, sd,
`2.5%`, `97.5%`, Rhat)

lor_array <- as.array(releff_FE)
OR_array <- exp(lor_array)
plot(OR_array, ref_line = 1) + theme(text = element_text(size=21.5))

forest_plot_FE <- plot(releff_FE, ref_line = 0) + OH_style() + theme(text =
element_text(size=21.5))
posterior_FE <- plot_prior_posterior(fit_FE, prior = c("intercept", "trt",
"reg"))
print(pred_FE <- predict(fit_FE, type = "response"))
pred_plot_FE <- plot(pred_FE, ref_line = c(0,1)) + OH_style() + theme(text
= element_text(size=21.5))

##################### 8.0 Fitting RE ML-NMR Models ----------------------
----

fit_RE <- nma(net_all,
              trt_effects = "random",
              link = "logit",
              likelihood = "bernoulli2",
              regression = ~(age + male + plc + npm1_positive)*.trt,
              class_interactions = "common",
              prior_het = half_normal(scale = 2.5),
              prior_intercept = normal(scale = 10),
              prior_trt = normal(scale = 10),
              prior_reg = normal(scale = 10),
```

```
              #iter = 50000,
              init_r = 0.1,
              int_thin = 1,
              QR = TRUE)

# We can investigate the divergent transitions in the RE model using pairs

pairs_plot_RE <- pairs(fit_RE,
                       pars = c("delta[Quantum: Quizartinib]",
                                "d[Quizartinib]",
                                "tau",
                                "lp__"))

# The divergent transition errors (red crosses) seem to be concentrated in
the upper tail of the heterogeneity standard deviation parameter.
# This suggests that the information to identify the heterogeneity
parameter is weak
# We have only 2 studies in the network - and that suggests a more
informative prior distribution might aid estimation.
# With only one study per comparison we can assume FE is acceptable

print(results_RE <- (fit_RE))
print(results_RE <- summary(fit_RE))
print(releff_RE <- relative_effects(fit_RE, all_contrasts = TRUE))

OR_RE <- releff_RE$summary %>% mutate(mean = round(exp(mean),4), sd =
round(exp(sd),4), `2.5%` = round(exp(`2.5%`),4),`25%` =
round(exp(`25%`),4), `50%` = round(exp(`50%`),5),`75%` =
round(exp(`75%`),5), `97.5%` = round(exp(`97.5%`),5))
OR_RE <- OR_RE %>% select(.study, .trtb, .trta, parameter, mean, `50%`, sd,
`2.5%`, `97.5%`, Rhat)

forest_plot_RE <- plot(releff_RE, ref_line = 0) + OH_style() + theme(text =
element_text(size=21.5))
posterior_RE <- plot_prior_posterior(fit_RE, prior = c("intercept", "trt",
"reg"))
#plot_integration_error(fit_RE_all)
print(pred_RE <- predict(fit_RE, type = "response"))
pred_plot_RE <- plot(pred_RE, ref_line = c(0,1)) + OH_style() + theme(text
= element_text(size=21.5))

# Model Comparison via DIC check

#FE
print(dic_FE <- dic(fit_FE))
resdev <- dic_FE[["resdev"]]
pd <- dic_FE[["pd"]]
dic <- dic_FE[["dic"]]
FE <- cbind("Model" = "FE", "Residual Deviance" = resdev, "pD" = pd, "DIC"
= dic)

# RE
print(dic_RE <- dic(fit_RE))
resdev <- dic_RE[["resdev"]]
pd <- dic_RE[["pd"]]
dic <- dic_RE[["dic"]]
RE <- cbind("Model" = "RE", "Residual Deviance" = resdev, "pD" = pd, "DIC"
= dic)
model_stats <- rbind.data.frame(FE,RE)
model_stats <- model_stats %>%
  mutate_at(vars(`Residual Deviance`, pD, DIC), as.numeric) %>%
```

```
  mutate_at(vars(`Residual Deviance`, pD, DIC), ~round(., 3))

# DIC values between the two models are almost identical
# Suggesting that there is little evidence for any residual heterogeneity.



## CIR ----------------------------------------------------------------

# Trial Names =
## QuANTUM-First - IPD, Quizartinib vs Placebo in AML with FLT-3-ITD
positive patients
## RATIFY - Based on Rucker et al, Midostaurin vs Placebo in AML with FLT3-
ITD positive patients

# 2.0 IPD data from Quantum First =================

adsl <- read_sas("adsl.sas7bdat") %>%
  select("AAGE", "ITTFL", "SEX", "RACE", "BLASTBL",
         "NEUTBL", "PLATBL", "FLT3CAT", "FLT3BL", "ANTHRTYP",
         "RISKSTAT", "USUBJID", "ECOGBL", "IVRSWBC", "WBCCNT",
         "WBCCOUNT", "NPM1MUT", "NPM1WILD")

adrs <- read_sas("adrs.sas7bdat") %>%
  select(USUBJID, TRTP, ADT2, AVAL, AVALC, CRDY, CRIDY)

adtte <- read_sas("adtte.sas7bdat") %>%
  select(treatment = "TRTPN", "AP01SDT", "USUBJID", "EVNTDESC",
         "AVAL", "ADT", "STARTDT", outcome = "PARAMCD",
         "RANDDT", "CNSR") %>%
  rename_all(tolower)

tem <- adsl %>%
  filter(ITTFL == "Y") %>%
  mutate(male = if_else(SEX == "M", 1, 0),
         female = if_else(SEX == "F", 1, 0),
         npm1_positive = if_else(NPM1MUT == "Y", 1, 0),
         ar_raw = (FLT3BL * 0.01) / (1 - (FLT3BL * 0.01)), # Convert VAF to
AR
         allelic_ratio_low = if_else(ar_raw <= 0.7, 1, 0)) %>%
  select(USUBJID, AAGE, PLATBL, NEUTBL, male, allelic_ratio_low,
npm1_positive) %>%

  group_by(USUBJID) %>%
  summarise(age = unique(AAGE),
            male = unique(male),
            plc = unique(PLATBL),
            anc = unique(NEUTBL),
            npm1_positive = unique(npm1_positive),
            allelic_ratio_low = unique(allelic_ratio_low)) %>%
  ungroup() %>%
  rename_all(tolower)

# Dataset based on Overall Survival - omit NAs
qOS <- adtte %>%
  filter(outcome == "OS1") %>%
  left_join(tem) %>%
  mutate(treatment = abs(treatment - 2))
qOS$study<-"Quantify"

# Dataset based on Cumulative incidence of relapse (CIR)
```

```
time_to_cr <- adrs %>%
  mutate(cr_status = case_when(is.na(CRDY) ~ 0,
                               CRDY <= 60 ~ 1,
                               CRDY > 60 ~ 0)) %>%
  select(USUBJID, TRTP, cr_status) %>%
  distinct(USUBJID, .keep_all = TRUE) %>%
  rename_all(tolower) %>%
  left_join(tem, by = "usubjid") %>%
  filter(cr_status == 1) %>%
  pull(usubjid)

cir_unadj <- adtte %>%
  filter(outcome == "DOCR") %>%
  filter(usubjid %in% time_to_cr) %>%
  left_join(tem, by = "usubjid") %>%
  mutate(treatment = abs(treatment - 2)) %>%
  mutate(tx = if_else(treatment == 0, "Placebo QuANTUM-First Unadjusted",
                      "Quizartinib QuANTUM-First Unadjusted")) %>%
  mutate(aval = aval/30.4375) %>%
  mutate(status = case_when(evntdesc == "Had CR, No Relapse, No Death Date"
~ 0,
                            evntdesc == "Relapse" ~ 1,
                            evntdesc == "Death" ~ 2)) %>%
  mutate(status = factor(status, 0:2, labels = c("Censor", "Relapse",
"Death"))) %>%
  mutate(cnsr_cir = case_when(evntdesc == "Had CR, No Relapse, No Death
Date" ~ 0,
                              evntdesc == "Relapse" ~ 1,
                              evntdesc == "Death" ~ 0))


cir_unadj$study<-"Quantum"
cir_unadj<-cir_unadj  %>%
  mutate(
    treatment2 = case_when(treatment == 0 ~ "Placebo",
                           treatment == 1 ~ "Quizartinib"),
    trtclass = case_when(treatment == 1 ~ "TKI",
                         treatment == 0 ~ "Placebo"))

cir_unadj<-cir_unadj %>% arrange(aval)

cc_plc<-complete.cases(cir_unadj[,"plc"])
cc_age<-complete.cases(cir_unadj[,"age"])
cc_npm1<-complete.cases(cir_unadj[,"npm1_positive"])
cir_unadj <- filter(cir_unadj, cc_plc&cc_age&cc_npm1)

tte_cir<-Surv(cir_unadj$aval,abs(cir_unadj$cnsr_cir))
kmfit = survfit(tte_cir~cir_unadj$treatment2)
kmfit
plot(kmfit)+
  OH_style()

#####CIR

# 3.0 RATIFY FLT3-ITD characteristics - Rucker et al
=======================

# ML-NMR Input for Aggregate Trial Data

## Overall Survival ===
```

```
ratify_midostaurin <- 230
ratify_placebo <- 222

ratify_os_hr <- 0.79
ratify_os_hr_lci <- 0.59
ratify_os_hr_uci <- 1.06
ratify_os_hr_log <- log(ratify_os_hr)
ratify_os_se <- (log(ratify_os_hr) - log(ratify_os_hr_lci))/qnorm(0.975)
ratify_os_var <- ratify_os_se ^ 2

## TEMs included for NICE Analysis: Age, Sex, NMP1 positive, Platelet count

## Age
age<-c(47,48)
age_sd<-c((59-19)/4,(60-18)/4)
## Sex
male<-c((ratify_midostaurin - 116)/ratify_midostaurin,(ratify_placebo -
130)/ratify_placebo)
## FLT3 - High vs low allelic ratio
allelic_ratio_low<-c(171/ratify_midostaurin, 170/ratify_placebo)
## Platelet count
plc<-c(50.5,49.5)
plc_sd<-c((461-2)/4,(342-8)/4)
## nmc positivie
nmc_pos <-  c((95/190),(108/168))
## Absolute neutrophil count (ANC)
anc<-c(2.2,2.3)
anc_sd<-c(55.9/4,55.9/4)

Treatment<-c("Midostaurin","Placebo")
#crr_r<- c(ratify_midostaurin_cr,ratify_placebo_cr)

study<-"RATIFY"
RAT.AgD<-data.frame(age, age_sd, male, allelic_ratio_low,
plc,plc_sd,anc,anc_sd, nmc_pos, Treatment,  study)

RAT.AgD <-RAT.AgD %>%
  mutate(
    trtclass = case_when(Treatment == "Midostaurin" ~ "TKI",
                         Treatment == "Placebo" ~ "Placebo"))

## Read in Pseudo IPD for Ratify

# ratify_TTE

jmd_mido <- read_csv("ITC_RATIFY_CIR/KM_IPD2023_JMD_Mido.csv")
jmd_placebo <- read_csv("ITC_RATIFY_CIR/KM_IPD2023_JMD_Placebo.csv")

jmdtkd_mido <- read_csv("ITC_RATIFY_CIR/KM_IPD2023_JMD_TKD_Mido.csv")
jmdtkd_placebo <- read_csv("ITC_RATIFY_CIR/KM_IPD2023_JMD_TKD_Placebo.csv")

tkd_mido <- read_csv("ITC_RATIFY_CIR/KM_IPD2023_TKD_Mido.csv")
tkd_placebo <- read_csv("ITC_RATIFY_CIR/KM_IPD2023_TKD_Placebo.csv")

mido<-rbind(jmd_mido,jmdtkd_mido,tkd_mido)
placebo<-rbind(jmd_placebo,jmdtkd_placebo,tkd_placebo)
mido$Treatment<-"Midostaurin"
placebo$Treatment<-"Placebo"
ratify_TTE<-rbind(mido,placebo)
ratify_TTE <- ratify_TTE %>%
```

```
  mutate(Event = case_when(censored == "FALSE" ~ 1,
                           censored == "TRUE" ~ 0))

ratify_TTE$study<-"RATIFY"

ratify_TTE <-ratify_TTE %>%
  mutate(
    trtclass = case_when(Treatment == "Midostaurin" ~ "TKI",
                         Treatment == "Placebo" ~ "Placebo"))

tte_rat_cir<-Surv(ratify_TTE$time,ratify_TTE$Event)
summary(tte_rat_cir)
kmfit_r = survfit(tte_rat_cir~ratify_TTE$Treatment)
kmfit_r
plot(kmfit_r)

##################### 4.0 Creating the Network ---------------------------

net <- combine_network(
  set_ipd(cir_unadj,
          study = study,
          trt = treatment2,
          Surv = tte_cir,
          trt_class = trtclass
  ),
  set_agd_surv(ratify_TTE,
               study = study,
               trt = Treatment,
               Surv=tte_rat_cir,
               trt_class = trtclass,
               covariates = RAT.AgD
  )
)

net

# We can plot the network figure using the following

net_plot <- plot(net, weight_nodes = TRUE, weight_edges = TRUE,
show_trt_class = TRUE) +
  ggplot2::theme(legend.position = "bottom", legend.box = "vertical")



###################### 5.0 Kaplan-Meiers ---------------------------------
-----------------------------------

net_km <- ggplot() +  geom_km(network = net) + facet_wrap(~.study) +
  labs(y = "Survival probability", x = "Time") +
  coord_cartesian(ylim = c(0, 1)) +
  OH_style() +
  theme(legend.position = "right", legend.box.spacing = unit(0, "lines"))

# Statistics
# Curves

##################### 6.0 Numerical Integration for ML-NMR ----------------
------------

net <- add_integration(net,
                       age = distr(qgamma, mean = age, sd = age_sd),
```

```
                       male = distr(qbern, prob = male),
                       # allelic_ratio_low = distr(qbern, prob =
allelic_ratio_low),
                       plc = distr(qgamma, mean = plc, sd = plc_sd),
                       # anc = distr(qgamma, mean = anc, sd = anc_sd),
                       npm1_positive= distr(qbern, prob = nmc_pos),
                       n_int = 50
)

#################### 7.0 Fitting FE & RE ML-NMR Models ------------------
---------

# First we fit FE ML-NMR models using the function nma() with weakly
informative priors

##### 7.1 Mspline ---------

fit <- list(
  FE = nma(net,
           trt_effects = "fixed",
           likelihood = "mspline",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           QR = TRUE,
           iter = 2000),
  RE = nma(net,
           trt_effects = "random",
           likelihood = "mspline",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           prior_het = half_normal(scale = 2.5),
           QR = TRUE,
           iter = 2000)
)

analysis_mspl <- list()

analysis_mspl$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5)) +
  + labs(y = "Cumulative Incidence", x = "Time (months)") + ylim(0,1)
analysis_mspl$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

# Manipulate surv curves to flip to cumulative incidence curves
analysis_mspl[["surv_plot"]][["FE"]][["data"]][["value"]] <- 1-
analysis_mspl[["surv_plot"]][["FE"]][["data"]][["value"]] # flips fitted
curves
analysis_mspl[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]]
<- 1-
analysis_mspl[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]]
#flips surv events
analysis_mspl[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]]
<- 1-
```

```
analysis_mspl[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]] #
flips the censoring markers

analysis_mspl$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_mspl$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_mspl$releff<- lapply(fit, relative_effects)

analysis_mspl$medsurv <- lapply(fit, predict, type = "median")

analysis_mspl$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_mspl$forest_plot <- lapply(analysis_mspl$loghr, plot)
analysis_mspl$forest_plot$FE <- analysis_mspl$forest_plot$FE + OH_style()
analysis_mspl$forest_plot$RE <- analysis_mspl$forest_plot$RE + OH_style()

analysis_mspl$looic <- lapply(fit, loo)


##### 7.2 Exponential ---------

fit <- list(
  FE = nma(net,
           trt_effects = "fixed",
           likelihood = "exponential",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           QR = TRUE,
           iter = 2000),
  RE = nma(net,
           trt_effects = "random",
           likelihood = "exponential",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           prior_het = half_normal(scale = 2.5),
           QR = TRUE,
           iter = 2000)
)

analysis_exp <- list()

analysis_exp$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5)) +
  + labs(y = "Cumulative Incidence", x = "Time (months)") + ylim(0,1)
analysis_exp$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

analysis_exp[["surv_plot"]][["FE"]][["data"]][["value"]] <- 1-
analysis_exp[["surv_plot"]][["FE"]][["data"]][["value"]] # flips fitted
curves
```

```
analysis_exp[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]] <-
1-analysis_exp[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]]
#flips surv events
analysis_exp[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]] <-
1-analysis_exp[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]]
# flips the censoring markers

analysis_exp$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_exp$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_exp$releff<- lapply(fit, relative_effects)

analysis_exp$medsurv <- lapply(fit, predict, type = "median")

analysis_exp$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_exp$forest_plot <- lapply(analysis_exp$loghr, plot)
analysis_exp$forest_plot$FE <- analysis_exp$forest_plot$FE + OH_style()
analysis_exp$forest_plot$RE <- analysis_exp$forest_plot$RE + OH_style()

analysis_exp$looic <- lapply(fit, loo)


##### 7.3 Weibull ---------

fit <- list(
  FE = nma(net,
           trt_effects = "fixed",
           likelihood = "weibull",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           QR = TRUE,
           iter = 2000),
  RE = nma(net,
           trt_effects = "random",
           likelihood = "weibull",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           prior_het = half_normal(scale = 2.5),
           QR = TRUE,
           iter = 2000)
)

analysis_wei <- list()

analysis_wei$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5)) +
  + labs(y = "Cumulative Incidence", x = "Time (months)") + ylim(0,1)
analysis_wei$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

# Manipulate surv curves to flip to cumulative incidence curves
```

```
analysis_wei[["surv_plot"]][["FE"]][["data"]][["value"]] <- 1-
analysis_wei[["surv_plot"]][["FE"]][["data"]][["value"]] # flips fitted
curves
analysis_wei[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]] <-
1-analysis_wei[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]]
#flips surv events
analysis_wei[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]] <-
1-analysis_wei[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]]
# flips the censoring markers

analysis_wei$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_wei$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_wei$releff<- lapply(fit, relative_effects)

analysis_wei$medsurv <- lapply(fit, predict, type = "median")

analysis_wei$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_wei$forest_plot <- lapply(analysis_wei$loghr, plot)
analysis_wei$forest_plot$FE <- analysis_wei$forest_plot$FE + OH_style()
analysis_wei$forest_plot$RE <- analysis_wei$forest_plot$RE + OH_style()

analysis_wei$looic <- lapply(fit, loo)

##### 7.4 Log-Normal ---------

fit <- list(
  FE = nma(net,
           trt_effects = "fixed",
           likelihood = "lognormal",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           QR = TRUE,
           iter = 2000),
  RE = nma(net,
           trt_effects = "random",
           likelihood = "lognormal",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           prior_het = half_normal(scale = 2.5),
           QR = TRUE,
           iter = 2000)
)

analysis_lnorm <- list()

analysis_lnorm$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5)) +
  + labs(y = "Cumulative Incidence", x = "Time (months)") + ylim(0,1)
analysis_lnorm$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))
```

```
# Manipulate surv curves to flip to cumulative incidence curves
analysis_lnorm[["surv_plot"]][["FE"]][["data"]][["value"]] <- 1-
analysis_lnorm[["surv_plot"]][["FE"]][["data"]][["value"]] # flips fitted
curves
analysis_lnorm[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]]
<- 1-
analysis_lnorm[["surv_plot"]][["FE"]][["layers"]][[3]][["data"]][["surv"]]
#flips surv events
analysis_lnorm[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]]
<- 1-
analysis_lnorm[["surv_plot"]][["FE"]][["layers"]][[4]][["data"]][["surv"]]
# flips the censoring markers

analysis_lnorm$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_lnorm$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_lnorm$releff<- lapply(fit, relative_effects)

analysis_lnorm$medsurv <- lapply(fit, predict, type = "median")

analysis_lnorm$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_lnorm$forest_plot <- lapply(analysis_lnorm$loghr, plot)
analysis_lnorm$forest_plot$FE <- analysis_lnorm$forest_plot$FE + OH_style()
analysis_lnorm$forest_plot$RE <- analysis_lnorm$forest_plot$RE + OH_style()

analysis_lnorm$looic <- lapply(fit, loo)

### 7.5 Model Fit LOOIC ----------------------------------------

model_comp <- loo_compare(analysis_mspl$looic$FE, analysis_mspl$looic$RE,
                          analysis_exp$looic$FE, analysis_exp$looic$RE,
                          analysis_wei$looic$FE, analysis_wei$looic$RE,
                          analysis_lnorm$looic$FE, analysis_lnorm$looic$RE)


model_stats <- cbind(
  `Mspline FE`     = analysis_mspl$looic$FE$estimates[, "Estimate"],
  `Mspline RE`     = analysis_mspl$looic$RE$estimates[, "Estimate"],
  `Exponential FE` = analysis_exp$looic$FE$estimates[, "Estimate"],
  `Exponential RE` = analysis_exp$looic$REestimates[, "Estimate"],
  `Weibull FE`     = analysis_wei$looic$FE$estimates[, "Estimate"],
  `Weibull RE`     = analysis_wei$looic$RE$estimates[, "Estimate"],
  `LogNorm FE`     = analysis_lnorm$looic$FE$estimates[, "Estimate"],
  `LogNorm RE`     = analysis_lnorm$looic$RE$estimates[, "Estimate"]
)


## OS ----------------------------------------------------------------------
-----


# Trial Names =
## QuANTUM-First - IPD, Quizartinib vs Placebo in AML with FLT-3-ITD
positive patients
## RATIFY - Based on Rucker et al, Midostaurin vs Placebo in AML with FLT3-
ITD positive patients

# 2.0 IPD data from Quantum First ==================
```

```
adsl <- read_sas("adsl.sas7bdat") %>%
  select("AAGE", "ITTFL", "SEX", "RACE", "BLASTBL",
         "NEUTBL", "PLATBL", "FLT3CAT", "FLT3BL", "ANTHRTYP",
         "RISKSTAT", "USUBJID", "ECOGBL", "IVRSWBC", "WBCCNT",
         "WBCCOUNT", "NPM1MUT", "NPM1WILD")

adrs <- read_sas("adrs.sas7bdat") %>%
  select(USUBJID, TRTP, ADT2, AVAL, AVALC, CRDY, CRIDY)

adtte <- read_sas("adtte.sas7bdat") %>%
  select(treatment = "TRTPN", "AP01SDT", "USUBJID", "EVNTDESC",
         "AVAL", "ADT", "STARTDT", outcome = "PARAMCD",
         "RANDDT", "CNSR") %>%
  rename_all(tolower)

tem <- adsl %>%
  filter(ITTFL == "Y") %>%
  mutate(male = if_else(SEX == "M", 1, 0),
         female = if_else(SEX == "F", 1, 0),
         npm1_positive = if_else(NPM1MUT == "Y", 1, 0),
         #     npm1_negative = if_else(NPM1WILD == "Y", 1, 0),
         ar_raw = (FLT3BL * 0.01) / (1 - (FLT3BL * 0.01)), # Convert VAF to
AR
         #      allelic_ratio_high = if_else(ar_raw > 0.7, 1, 0),
         allelic_ratio_low = if_else(ar_raw <= 0.7, 1, 0)) %>%
  select(USUBJID, AAGE, PLATBL, NEUTBL, male, allelic_ratio_low,
npm1_positive) %>%
  #select(USUBJID, AAGE, PLATBL, NEUTBL, male, allelic_ratio_low) %>%

  group_by(USUBJID) %>%
  summarise(age = unique(AAGE),
            male = unique(male),
            plc = unique(PLATBL),
            anc = unique(NEUTBL),
            npm1_positive = unique(npm1_positive),
            allelic_ratio_low = unique(allelic_ratio_low)) %>%
  ungroup() %>%
  rename_all(tolower)

# Dataset based on Overall Survival

os_completecases <- "Complete Cases" # TODO: Select any one of:  "Complete
Cases" OR "Imputation"

qOS <- adtte %>%
  filter(outcome == "OS1") %>%
  left_join(tem) %>%
  mutate(treatment = abs(treatment - 2))
#  filter(age <= 60)
qOS$study<-"Quantum"

if(os_completecases == "Imputation") {
  data <- qOS[,c("plc","age","male","treatment","anc","allelic_ratio_low",
"npm1_positive")] # Read in dataset an exclude ID variable
  data$male = as.factor(data$male)
  data$allelic_ratio_low = as.factor(data$allelic_ratio_low)
  imp <- mice(data, m=5, maxit=20)

  imp$method
  qOS_new<-complete(imp, action = 1)
```

```
  qOS_new$allelic_ratio_low = as.numeric(qOS_new$allelic_ratio_low)-1

  qOS<-
cbind(qOS[,c("usubjid","treatment","age","male","study","aval","cnsr",
"study", "trtclass",
"npm1_positive")],qOS_new[,c("plc","anc","allelic_ratio_low")])

}

if(os_completecases == "Complete Cases") {
  #cc_arl<-complete.cases(qOS[,"allelic_ratio_low"])
  cc_plc<-complete.cases(qOS[,"plc"])
  cc_age<-complete.cases(qOS[,"age"])
  cc_npm1<-complete.cases(qOS[,"npm1_positive"])
  qOS <- filter(qOS, cc_plc&cc_age&cc_npm1)  ## 3 observations dropped
}

## cnrs death = 0 still; make sure to adjust for surv
qOS<-qOS  %>%
  mutate(
    treatment2 = case_when(treatment == 0 ~ "Placebo",
                           treatment == 1 ~ "Quizartinib"),
    trtclass = case_when(treatment == 1 ~ "TKI",
                         treatment == 0 ~ "Placebo"))

library("survival")
tte<-Surv(qOS$aval,abs(qOS$cnsr-1))
tte


# 3.0 RATIFY FLT3-ITD characteristics - Rucker et al
=======================

# ML-NMR Input for Aggregate Trial Data

## Overall Survival ===

ratify_midostaurin <- 230
ratify_placebo <- 222

ratify_os_hr <- 0.79
ratify_os_hr_lci <- 0.59
ratify_os_hr_uci <- 1.06
ratify_os_hr_log <- log(ratify_os_hr)
ratify_os_se <- (log(ratify_os_hr) - log(ratify_os_hr_lci))/qnorm(0.975)
ratify_os_var <- ratify_os_se ^ 2

## TEMs included for NICE Analysis: Age, Sex, NMP1 positive, Platelet count

#crr_n<-c(ratify_midostaurin,ratify_placebo)
## Age
age<-c(47,48)
age_sd<-c((59-19)/4,(60-18)/4)
## Sex
male<-c((ratify_midostaurin - 116)/ratify_midostaurin,(ratify_placebo -
130)/ratify_placebo)
## FLT3 - High vs low allelic ratio
allelic_ratio_low<-c(171/ratify_midostaurin, 170/ratify_placebo)
## Platelet count
plc<-c(50.5,49.5)
plc_sd<-c((461-2)/4,(342-8)/4)
```

```
## nmc positivie
nmc_pos <-  c((95/190),(108/168))
## Absolute neutrophil count (ANC)
anc<-c(2.2,2.3)
anc_sd<-c(55.9/4,55.9/4)

Treatment<-c("Midostaurin","Placebo")

study<-"RATIFY"
RAT.AgD<-data.frame(age, age_sd, male, allelic_ratio_low,
plc,plc_sd,anc,anc_sd, nmc_pos, Treatment, ratify_os_hr , ratify_os_se ,
study)

RAT.AgD <-RAT.AgD %>%
  mutate(
    trtclass = case_when(Treatment == "Midostaurin" ~ "TKI",
                         Treatment == "Placebo" ~ "Placebo"))

## Read in Pseudo IPD for Ratify

digitized <- read_csv("Rucker_IPD_Digitized.csv")

digitized <- digitized %>%
  mutate(USUBJID = 1:nrow(digitized),
         USUBJID = as.character(USUBJID)) %>%
  mutate(CNSR = abs(Event - 0), # Changed this to 0 instead of 1 seemed to
fix issues with curves
         WEIGHT = 1,
         Treatment = case_when(Treatment == "Placebo" ~ "Placebo",
                               Treatment == "Midostaurin" ~ "Midostaurin"))
%>%
  mutate(time = time * DAYS_IN_MONTH) # Changed time for RATIFY to days

ratify_TTE <- TTE(digitized)

ratify_TTE_summary <- summary(ratify_TTE, groups = "Treatment") %>%
  format_doubles()

ratify_TTE_hazards <- ratify_TTE  %>%
  hazard_ratio(covariates = "Treatment") %>%
  format_doubles(decimals = 8)

RAT_TTE<-Surv(digitized$time,digitized$CNSR)

library("survival")
tte<-Surv(qOS$aval,abs(qOS$cnsr-1))
tte
ratify_TTE$study<-"RATIFY"

ratify_TTE <-ratify_TTE %>%
  mutate(
    trtclass = case_when(Treatment == "Midostaurin" ~ "TKI",
                         Treatment == "Placebo" ~ "Placebo"))

ratify_TTE

#################### 4.0 Creating the Network ----------------------------

net <- combine_network(
  set_ipd(qOS,
          study = study,
```

```
          trt = treatment2,
          Surv = tte,
          trt_class = trtclass
  ),
  set_agd_surv(ratify_TTE,
               study = study,
               trt = Treatment,
               Surv=RAT_TTE,
               trt_class = trtclass,
               covariates = RAT.AgD
  )
)

net

# We can plot the network figure using the following

net_plot <- plot(net, weight_nodes = TRUE, weight_edges = TRUE,
show_trt_class = TRUE) +
  ggplot2::theme(legend.position = "bottom", legend.box = "vertical")

###################### 5.0 Kaplan-Meiers ---------------------------------
-------------------------------------

net_km <- ggplot() +  geom_km(network = net) + facet_wrap(~.study) +
  labs(y = "Survival probability", x = "Time") +
  coord_cartesian(ylim = c(0, 1)) +
  OH_style() +
  theme(legend.position = "right", legend.box.spacing = unit(0, "lines"))



###################### 6.0 Numerical Integration for ML-NMR ----------------
------------

net <- add_integration(net,
                       age = distr(qgamma, mean = age, sd = age_sd),
                       male = distr(qbern, prob = male),
                       # allelic_ratio_low = distr(qbern, prob =
allelic_ratio_low),
                       plc = distr(qgamma, mean = plc, sd = plc_sd),
                       # anc = distr(qgamma, mean = anc, sd = anc_sd),
                       npm1_positive= distr(qbern, prob = nmc_pos),
                       n_int = 50
)

###################### 7.0 Fitting FE & RE ML-NMR Models -------------------
---------

# First we fit FE ML-NMR models using the function nma() with weakly
informative priors

##### 7.1 Mspline ---------

fit <- list(
  FE = nma(net,
           trt_effects = "fixed",
           likelihood = "mspline",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
```

```
            prior_trt = normal(0, 100),
            prior_reg = normal(0, 100),
            prior_aux = half_normal(1),
            QR = TRUE,
            iter = 2000),
  RE = nma(net,
            trt_effects = "random",
            likelihood = "mspline",
            regression = ~(age + male + plc + npm1_positive)*.trt,
            #class_interactions = "common",
            prior_intercept = normal(0, 100),
            prior_trt = normal(0, 100),
            prior_reg = normal(0, 100),
            prior_aux = half_normal(1),
            prior_het = half_normal(scale = 2.5),
            QR = TRUE,
            iter = 2000)
)

analysis_mspl <- list()

analysis_mspl$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))
analysis_mspl$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

analysis_mspl$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_mspl$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_mspl$releff<- lapply(fit, relative_effects)

analysis_mspl$medsurv <- lapply(fit, predict, type = "median")

analysis_mspl$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_mspl$forest_plot <- lapply(analysis_mspl$loghr, plot)
analysis_mspl$forest_plot$FE <- analysis_mspl$forest_plot$FE + OH_style()
analysis_mspl$forest_plot$RE <- analysis_mspl$forest_plot$RE + OH_style()

analysis_mspl$looic <- lapply(fit, loo)


##### 7.2 Exponential ---------

fit <- list(
  FE = nma(net,
            trt_effects = "fixed",
            likelihood = "exponential",
            regression = ~(age + male + plc + npm1_positive)*.trt,
            #class_interactions = "common",
            prior_intercept = normal(0, 100),
            prior_trt = normal(0, 100),
            prior_reg = normal(0, 100),
            prior_aux = half_normal(1),
            QR = TRUE,
            iter = 2000),
  RE = nma(net,
            trt_effects = "random",
            likelihood = "exponential",
            regression = ~(age + male + plc + npm1_positive)*.trt,
```

```
            #class_interactions = "common",
            prior_intercept = normal(0, 100),
            prior_trt = normal(0, 100),
            prior_reg = normal(0, 100),
            prior_aux = half_normal(1),
            prior_het = half_normal(scale = 2.5),
            QR = TRUE,
            iter = 2000)
)

analysis_exp <- list()

analysis_exp$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))
analysis_exp$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

analysis_exp$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_exp$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_exp$releff<- lapply(fit, relative_effects)

analysis_exp$medsurv <- lapply(fit, predict, type = "median")

analysis_exp$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_exp$forest_plot <- lapply(analysis_exp$loghr, plot)
analysis_exp$forest_plot$FE <- analysis_exp$forest_plot$FE + OH_style()
analysis_exp$forest_plot$RE <- analysis_exp$forest_plot$RE + OH_style()

analysis_exp$looic <- lapply(fit, loo)


##### 7.3 Weibull ---------

fit <- list(
  FE = nma(net,
            trt_effects = "fixed",
            likelihood = "weibull",
            regression = ~(age + male + plc + npm1_positive)*.trt,
            #class_interactions = "common",
            prior_intercept = normal(0, 100),
            prior_trt = normal(0, 100),
            prior_reg = normal(0, 100),
            prior_aux = half_normal(1),
            QR = TRUE,
            iter = 2000),
  RE = nma(net,
            trt_effects = "random",
            likelihood = "weibull",
            regression = ~(age + male + plc + npm1_positive)*.trt,
            #class_interactions = "common",
            prior_intercept = normal(0, 100),
            prior_trt = normal(0, 100),
            prior_reg = normal(0, 100),
            prior_aux = half_normal(1),
            prior_het = half_normal(scale = 2.5),
            QR = TRUE,
            iter = 2000)
)
```

```
analysis_wei <- list()

analysis_wei$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))
analysis_wei$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

analysis_wei$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
analysis_wei$haz_plot$RE <- plot(predict(fit$RE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_wei$releff<- lapply(fit, relative_effects)

analysis_wei$medsurv <- lapply(fit, predict, type = "median")

analysis_wei$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_wei$forest_plot <- lapply(analysis_wei$loghr, plot)
analysis_wei$forest_plot$FE <- analysis_wei$forest_plot$FE + OH_style()
analysis_wei$forest_plot$RE <- analysis_wei$forest_plot$RE + OH_style()

analysis_wei$looic <- lapply(fit, loo)

##### 7.4 Log-Normal ---------

fit <- list(
  FE = nma(net,
           trt_effects = "fixed",
           likelihood = "lognormal",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           QR = TRUE,
           iter = 2000),
  RE = nma(net,
           trt_effects = "random",
           likelihood = "lognormal",
           regression = ~(age + male + plc + npm1_positive)*.trt,
           #class_interactions = "common",
           prior_intercept = normal(0, 100),
           prior_trt = normal(0, 100),
           prior_reg = normal(0, 100),
           prior_aux = half_normal(1),
           prior_het = half_normal(scale = 2.5),
           QR = TRUE,
           iter = 2000)
)

analysis_lnorm <- list()

analysis_lnorm$surv_plot$FE <- plot(predict(fit$FE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))
analysis_lnorm$surv_plot$RE <- plot(predict(fit$RE, type = "survival")) +
OH_style() + geom_km(net) + theme(text = element_text(size=21.5))

analysis_lnorm$haz_plot$FE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))
```

```
analysis_lnorm$haz_plot$RE <- plot(predict(fit$FE, type = "hazard", level =
"aggregate")) + OH_style() + theme(text = element_text(size=21.5))

analysis_lnorm$releff<- lapply(fit, relative_effects)

analysis_lnorm$medsurv <- lapply(fit, predict, type = "median")

analysis_lnorm$loghr <- lapply(fit,relative_effects, all_contrasts = TRUE)
analysis_lnorm$forest_plot <- lapply(analysis_lnorm$loghr, plot)
analysis_lnorm$forest_plot$FE <- analysis_lnorm$forest_plot$FE + OH_style()
analysis_lnorm$forest_plot$RE <- analysis_lnorm$forest_plot$RE + OH_style()

analysis_lnorm$looic <- lapply(fit, loo)

### 7.5 Model Fit LOOIC ----------------------------------------

model_comp <- loo_compare(analysis_mspl$looic$FE, analysis_mspl$looic$RE,
                          analysis_exp$looic$FE, analysis_exp$looic$RE,
                          analysis_wei$looic$FE, analysis_wei$looic$RE,
                          analysis_lnorm$looic$FE, analysis_lnorm$looic$RE)

model_stats <- cbind(
  `Parameter`      = c("elpd_loo", "p_loo", "LOOIC"),
  `Mspline FE`     = analysis_mspl$looic$FE$estimates[, "Estimate"],
  `Mspline RE`     = analysis_mspl$looic$RE$estimates[, "Estimate"],
  `Exponential FE` = analysis_exp$looic$FE$estimates[, "Estimate"],
  `Exponential RE` = analysis_exp$looic$REestimates[, "Estimate"],
  `Weibull FE`     = analysis_wei$looic$FE$estimates[, "Estimate"],
  `Weibull RE`     = analysis_wei$looic$RE$estimates[, "Estimate"],
  `LogNorm FE`     = analysis_lnorm$looic$FE$estimates[, "Estimate"],
  `LogNorm RE`     = analysis_lnorm$looic$RE$estimates[, "Estimate"]
)
```

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Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
Quizartinib EAG clarification questions	**1.0_Amend**	**Yes**	**17/05/2024**

Section A: Clarification on effectiveness data

A9. Priority Question: Sorafenib maintenance therapy is a recommended by the NHS as a maintenance treatment option for adults with *FLT3-ITD*+ AML post HSCT. Clinical advice to the EAG indicated that it is now widely used in this population.

c. Please provide an indirect treatment comparison of quizartinib with sorafenib maintenance therapy for adults with *FLT3-ITD*+ AML post HSCT.

Feasibility assessment

A top-line feasibility assessment of an indirect treatment comparison (ITC) of quizartinib vs sorafenib using cumulative incidence of relapse (CIR) and overall survival (OS) data from the QuANTUM-First trial and several sorafenib trials post allogeneic haematopoietic stem cell transplantation (allo-HSCT) was conducted focussing on trial differences and the quality of evidence that can be generated from an ITC. The alignment of inclusion and exclusion criteria between the trials was assessed to identify differences between the trials and understand if individual patient-level data (IPD) of QuANTUM-First can be modified to match that of the sorafenib trials. Baseline characteristics were compared to assess if there is enough heterogeneity to support the rationale for conducting a matching-adjusted indirect treatment comparison (MAIC), and a sufficient number of parameters available for matching, making it technically feasible to conduct the MAIC. Differences were reviewed for outcomes measured, length of study, and follow-up periods, which would influence the comparability of study outcomes. Heterogeneity in study design and conduct were noted to identify bias introduced by differences across the trials that cannot be adjusted for. Two sorafenib studies were assessed, SORMAIN (1) and Xuan/Xu et al. (2, 3), in line with the 2023 National health Service (NHS) evidence review of sorafenib maintenance for FLT3-internal tandem duplication (FLT3-ITD) acute myeloid leukaemia (AML) undergoing allo-HSCT (4). A third study by Loo et al. (5) was identified but not included in the assessment, as the outcomes reported were not suitable for the desired analyses.

Differences in the inclusion criteria between QuANTUM-First and Xuan/Xu et al. were the age restrictions used, which were narrower in Xuan/Xu et al. than in QuANTUM-First (18-60 years versus 18-75 years). Additionally, Xuan/Xu et al. allowed for patients to be treated with sorafenib before transplantation, which is not in line with United Kingdom (UK) guidelines where sorafenib is only used after transplant. Another important trial characteristic in Xuan/Xu et al. was the open label design, wherein patients either received open label sorafenib treatment or no maintenance treatment. The Xuan/Xu et al. trial was conducted exclusively in China, raising questions about the transferability of results from the Chinese setting to the UK,

considering potential influences of race on AML treatment response, as well as in terms of differences in local treatment practices. Finally, patients needed to be in complete remission (CR) before and after HSCT, which differed from QuANTUM-First where patients with and without CR were eligible for HSCT as well as for maintenance treatment. The trial reported OS and CIR outcomes suitable for analysis. A minor difference in study design was the dosing of sorafenib in Xuan/Xu et al. which was 400mg orally twice daily whereas in the UK, standard dosing would start with 400mg daily and increase to 400mg orally twice daily after 6 weeks.

A relevant difference in the inclusion criteria between QuANTUM-First and SORMAIN was the restriction in SORMAIN to patients who achieved CR post-HSCT in order to receive sorafenib maintenance treatment, which was not imposed in QuANTUM-First. A meaningful limitation of the SORMAIN trial was the sample size of 83 patients, which represented 44% of the targeted sample size of the trial according to the power calculations. Due to difficulties in recruitment, patient recruiting was discontinued prior to inclusion of a sufficient sample size. The trial was therefore underpowered. The trial reported OS outcomes suitable for analysis.

Table 1. Summary of the trial characteristics of QuANTUM-First, SORMAIN, and Xuan/Xu et al.

Trial	QuANTUM-First (6)	SORMAIN (1)	Xuan et al. 2020 & Xu et al. 2022 (2, 3)
Eligible patient population	Patients 18 to 75 years of age, who had newly diagnosed *FLT3-ITD* (+) AML.	Adults with *FLT3-ITD* AML after allo-HSCT.	Adults with *FLT3-ITD* AML after allo-HSCT aged 18-60.
Investigated treatments	Quizartinib as continuation therapy Maintenance treatment started 30 to 180 days post-transplant.	Sorafenib 2 x 200mg orally per day for 2 weeks, then 3 x 200mg orally per day for 4 weeks, then 4 x 200mg orally per day. Treatment started between 60 and 100 days after allo-HSCT and continued for 24 months or until relapse or intolerable toxicity. Median duration of sorafenib treatment was 35 weeks.	Sorafenib 400mg orally twice daily. Dose reductions or interruptions allowed if adverse events of grade ≥ occurred. Treatment started between 30 and 60 days after allo-HSCT and continued up to 180 days post-HSCT. Approximately 58% of patients received sorafenib pre-transplant. Median duration of sorafenib treatment was 19 weeks.
Comparators	Placebo during continuation phase.	Placebo for up to 24 months.	No maintenance therapy with sorafenib or another FLT3-inhibitor.
Location	International	Germany, Austria	China
Treatment history of post-HSCT maintenance patients	Patients treated with HSCT during or after consolidation, with or without prior achievement of CR.	HSCT could be given as part of consolidation therapy upfront or in the context of R/R AML, with or without prior achievement of complete remission. Post-HSCT, patients had to be in complete hematologic remission.	Patients had to have CR before and after HSCT, and hematologic recovery within 60 days post-transplantation.
Primary outcome	OS	OS, measured from randomization (enrolment tool place after HSCT), RFS	Infections, OS, measured from transplantation, CIR
Trial design			
Randomization	1:1, stratified by age, region, and WBC	1:1	1:1
Blinding	Double-blinded	Double-blinded	Open label
Median follow-up time	39 months	42 months	37 months
Sample size	539	83*	202
Prior and Concomitant therapy	No prior or concomitant therapy, with exceptions.	Patients could be treated with TKIs (including sorafenib), chemotherapy or a second allo-HSCT for the treatment of relapse after study entry.	GVHD and infection prophylaxis were permitted. Patients could be treated with TKIs (including sorafenib), chemotherapy or donor lymphocyte infusion after relapse.

Abbreviations: CIR, cumulative incidence of relapse; CR, complete remission; *FLT3-ITD* AML, FMS-Like Tyrosine Kinase 3-internal-tandem-duplication-positive Acute Myeloid Leukemia; GVHD, graft-versus-host-disease; OS, Overall Survival; HSCT, hematopoietic cell transplantation; RFS, relapse-free survival; R/R, relapsed or refractory; TKI, Tyrosine Kinase Inhibitor, WBC, white blood cell count.
Note: * Study did not reach the calculated sample size needed

Table 2. Summary of the patient characteristics from the QuANTUM-First, SORMAIN, and Xuan/Xu et al. studies in the quizartinib and sorafenib arm

	QuANTUM-First, Quizartinib, protocol specified HSCT followed by maintenance (N = 70)	SORMAIN, Sorafenib (N = 43)	Xuan et al. 2020 Xu et al. 2022, Sorafenib (N = 100)
Median age (range), years	xx (xx, xx)	54.2 (23, 75)	35 (18, 60)
Gender, Female, n (%)	xx (xx.x)	25 (58)	50 (50)
ECOG			
0	xx (xx)	13 (30)	Not reported
1	xx (xx)	29 (67)	Not reported
Platelets, Median (10^9/L)	xxx (xx, xxx)	143 (70, 408)	Not reported
Cytogenetic risk			
Low	x (x.x)	0 (0)	6 (6)
Intermediate	xx (xx.x)	40 (93)	80 (80)
High	x (xx.x)	1 (2)	7 (7)
Unknown	x (xx.x)	2 (4.7)	7 (7)
White blood cell count (10^3/µL)			
Median (10^9/L)	x.x (x.x, xx.x)	4.6 (1.9, 12.8)	54.8 (1.3, 463.0)
NPM1 mutation, n (%)	xx (xx.x)	29 (60)	29 (29)
Source	(6)	(1)	(2, 3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NPM1, Nucleophosmin 1.

The number of baseline characteristics available for assessment and potential matching was limited. Comparing the SORMAIN sorafenib arm to the QuANTUM-First quizartinib arm in maintenance post protocol-specified HSCT, most characteristics were comparable. SORMAIN included fewer patients with high cytogenic risk and a higher proportion of patients with NPM1 mutation.

Comparing the Xuan/Xu sorafenib arm to the QuANTUM-First quizartinib arm in maintenance post protocol-specified HSCT, the main difference was a considerably lower baseline age with a median of 35 years in Xuan/Xu et al. compared to a median of xx years in QuANTUM-First. Additionally, the fraction of patients with an NPM1 mutation was lower in Xuan/Xu et al. (29% versus 43%). Fewer characteristics were available for comparison.

An ITC of quizartinib versus sorafenib using evidence from SORMAIN was therefore considered more robust compared to using evidence from Xuan/Xu et al. . Using evidence from Xuan/Xu et al. was not preferred considering the heterogeneity in patients' age compared to the quizartinib arm and the restriction to patients with CR before and after transplant. Additionally, the study deviated from UK clinical practice considering sorafenib was used before transplant, and differences were suspected to exist in terms of clinical practice due to a difference in location, further biasing a potential comparison against QuANTUM-First.

Given the limited sample size of the quizartinib maintenance post-HSCT arm, challenges may be anticipated to achieve successful matching of the quizartinib arm's population to the

SORMAIN sorafenib arm. The matched results may be influenced by individual patients to an undue extent. Due to availability of published data from SORMAIN, only an ITC of OS in maintenance post-HSCT can be conducted.

ITC methods

The ITC methodology for matching QuANTUM-First's population to patient populations from other trials has been described previously in the submission documents. Given the placebo arm of the QuANTUM-First trial could not be used as an anchor, as randomization was broken between baseline and beginning of maintenance, an unanchored MAIC was used. Patients entering maintenance treatment in QuANTUM-First had previously been randomized at the start of the trial, but experienced induction, consolidation and transplant treatment in the meantime. Therefore, the probability of entering into post-HSCT maintenance was affected by the treatment received, and patients entering post-HSCT maintenance treatment in the placebo and the quizartinib arms could not be considered to be randomized anymore. Consequently, relative treatment effects could not be estimated for quizartinib versus placebo in QuANTUM-First, and an unanchored ITC was needed, comparing the quizartinib arm directly against the sorafenib arm. In addition to matching for treatment effect modifying characteristics, unanchored ITCs additionally match for prognostic variables, in accordance with NICE TSD 18 (7).

Methods described in the company submission were generally followed, with exceptions outlined here. The same set of TEMs were used as in the original MAIC. Cytogenetic risk and ECOG performance status were considered as prognostic factors. Both TEMs and prognostic factors were confirmed by clinical opinion of their relevance. All variables matched on in the unanchored ITC are listed in Table 3. The matching was conducted as described in the company submission. The only outcome analysed was OS.

Table 3. Variables for matching used in the unanchored MAIC of quizartinib vs sorafenib

TEMs	**Values**
Age*	Continuous (median years)
Sex	Female, male
Platelet count*	Continuous (median 10^9/L)
NPM1 mutation	Yes, no
WBC*	Continuous (median 10^9/L)
Predictive factors	**Values**
Cytogenetic risk	Low, intermediate, high
ECOG performance*	0, ≥1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NPM1, Nucleophosmin 1; TEM, treatment-effect modifier; WBC, white blood-cell count.
Notes:* At beginning of maintenance.

Cox Proportional Hazards models with treatment as the sole covariate were fit to pseudo IPD of SORMAIN and to the weighted IPD from QuANTUM-First to calculate a HR for OS.

Results

All TEMs and prognostic factors were included for matching. The estimated sample size (ESS) after matching was xx.x (xx% of the initial sample size) and of sufficient size according to guidelines. Table 4 shows the characteristics of patients on quizartinib and sorafenib in the post-HSCT maintenance state before matching, and the reweighted characteristics for patients on quizartinib after matching. After matching, minor imbalances were still present as seen for platelet count, NPM1 mutation status and WBC count. Major imbalances that were observed before matching, for example for high cytogenetic risk and ECOG, were no longer present.

Table 4. Summary of patient characteristics before and after matching for quizartinib (QuANTUM-First quizartinib arm with protocol-specified HSCT followed by maintenance treatment) and sorafenib (SORMAIN)

TEM / Prognostic variable	Quizartinib (N = 70)	Quizartinib, weighted (ESS = xx.xx [xx%])	Sorafenib (N = 43)
Median age (range), years	xx (xx, xx)	xx (xx, xx)	54.2 (23, 75)
Gender, Female, n (%)	xx (xx.xx)	xx.xx (xx.x)	25 (58.14)
ECOG Performance score			
0	xx (xx.xx)	xx.xx (xx.x)	13 (30.32)
1 or above	xx (xx.xx)	xx.xx (xx.x)	29 (67.44)
Platelets, Median (10^9/L)	xxx (xx, xxx)	xxx (xx, xxx)	143 (70, 408)
Cytogenetic risk			
Low	x (x.xx)	x.x (x.x)	0 (0)
Intermediate	xx (xx.xx)	xx.xx (xx.x)	40 (93)
High	x (xx.xx)	x.xx (x.x)	1 (2)
Unknown	x (xx.x)	x.xx (x.x)	2 (4.65)
WBC Count Median (10^9/L)	x.xx (x.xx, xx.xx)	x.x (x.x, xx.x)	4.62 (1.88, 12.75)
NPM1 mutation, n (%)	xx (xx.xx)	xx.xx (xx.x)	29 (60)

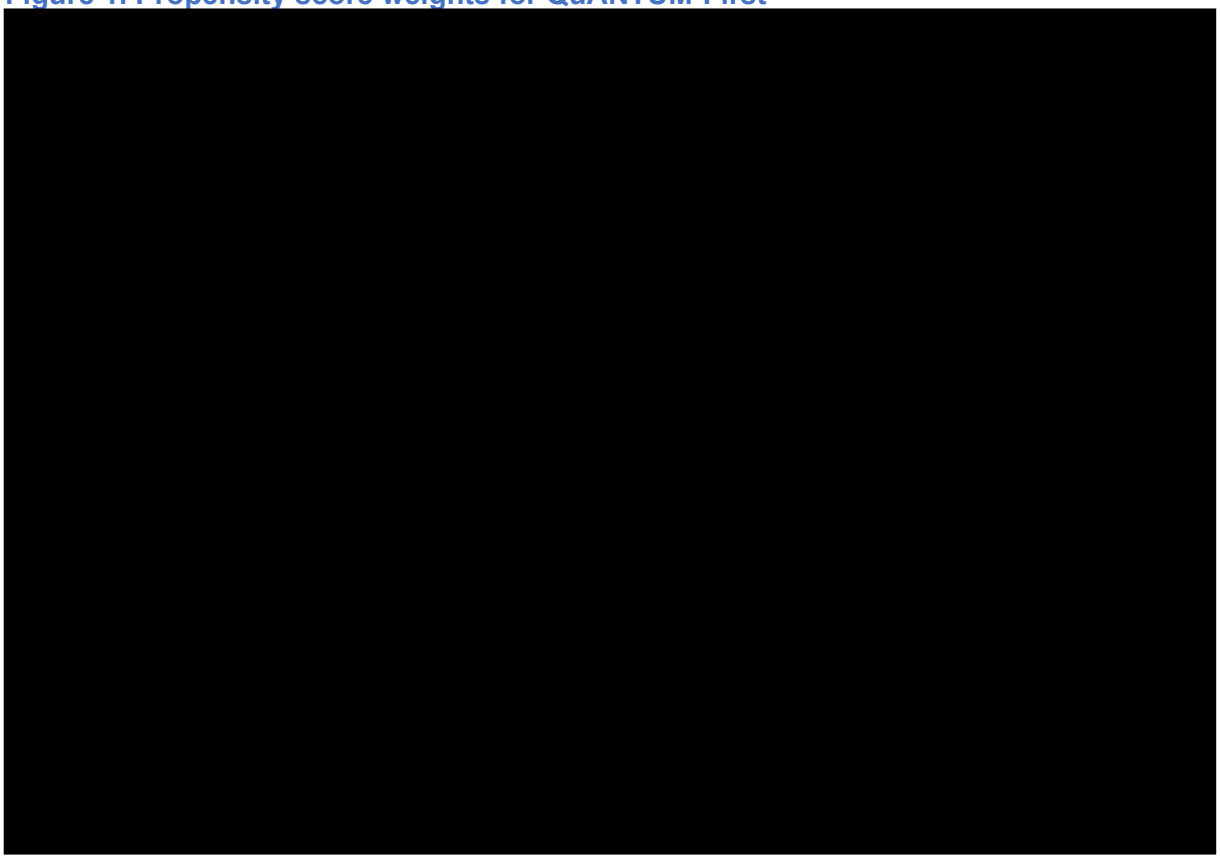
Abbreviations: ECOG, Eastern Cooperative Oncology Group ; ESS, estimated sample size; NPM1, Nucleophosmin 1; TEM, treatment-effect modifier; WBC, white blood-cell count.
Source: Daiichi Sankyo, 2024 (6)

The weights resulting from the unanchored MAIC were distributed homogenously with the majority of weights ranging within an acceptable range between 0 and 2, centred around 1 as shown in Table 5 and Figure 1. The highest observed weight was 2.9.

Table 5. Summary of propensity score weights for QuANTUM-First

Minimum	First Quartile	Median	Mean	Third Quartile	Maxiunn
x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

Figure 1. Propensity score weights for QuANTUM-First



Abbreviations: IPD, individual patient data; MAIC, matching adjusted indirect comparison.
Source: Daiichi Sankyo, 2024 (6).

Median OS was not reached for both quizartinib and sorafenib prior to matching or after matching, as both treatment arms presented with immature data. The matched and unmatched OS curves for quizartinib as well as the sorafenib OS curve can be seen in Figure 2. Comparing the weighted to the unweighted quizartinib curve, weighting shifted the quizartinib curve upwards during the first 38 months, and downwards during the following period.

The comparison of the matched quizartinib and the sorafenib curve indicated xx xxxxxxxxxx in OS during maintenance post-HSCT until at approximately xx months. At xx months, the xxxxxxxxxxx xxxxx xxxxxxx xxxxxxxx xxxxx xxx xxxxxxxxx xxxxx, however, it should be noted that the number of patients at risk in the quizartinib arm past 36 months was low given the limited follow-up time, and matching may have a larger impact on the tail of the quizartinib OS curve. The matched quizartinib and sorafenib curves seemed to align again at 50 months.

The HR for OS during maintenance post HSCT between quizartinib vs sorafenib obtained from the unanchored MAIC was x.xx (95% CI: x.xx, x.xx), xxxxxxxxxx xx xxxxxxxxxxxx xxxxxxxxx xxxxxxx xx xxxxxxxxx xxxx xxxxxxxxxx (Table 6). This is also reflected in the 95% CI of the KM curves, which did not show any differentiation of the treatment arms at any time. Landmark

survival at xx months was xx.x% in the weighted quizartinib arm as well as the sorafenib arm; the HR was x.xx (95% CI: x.xx, x.xx). The naïve HR between quizartinib and sorafenib during maintenance post HSCT was x.xx (95% CI: x.xx, x.xx).

Figure 2. OS curves during maintenance post-HSCT for matched quizartinib and sorafenib

Abbreviations: HCST, hematopoietic cell transplantation; OS, Overall Survival.
Source: Daiichi Sankyo, 2024 (6).

Table 6. Overall survival during maintenance post-HSCT - quizartinib vs sorafenib

Method	Comparison	Hazard ratio (95% CI)
Naïve	Quizartinib vs Sorafenib	x.xx (x.xx, x.xx)
unanchored MAIC[a]	Quizartinib vs Sorafenib	x.xx (x.xx, x.xx)

Abbreviations: CI, Confidence interval; MAIC, matching adjusted indirect comparison.
Notes: [a] CI was computed using the robust sandwich variance estimation.

Section B: Clarification on cost-effectiveness data

B9. Priority Question: Please utilise the analysis requested in question A9c to conduct a scenario analysis exploring the cost-effectiveness of treatment sequences that include post-HSCT maintenance therapy with sorafenib.

For reference, the company base case is presented in Table 7.

Table 7. Incremental cost-effectiveness results (deterministic base-case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,459
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,364

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

An exploratory scenario was conducted by utilizing the analysis results requested in A9c. In this exploratory scenario, sorafenib was considered in treatment sequences for post-HSCT maintenance therapy, which means that sorafenib was allowed to be used in both the midostaurin and SC regimen.

The comparative survival efficacy of sorafenib in post-HSCT maintenance was obtained by applying the HR (quizartinib vs sorafenib xx=x.xx [95% CI: x.xx, x.xx]) conducted by the unanchored MAIC requested in A9c. The quizartinib post-HSCT survival was selected as the reference arm, which is sourced from the patients (company base case population) who received protocol-specified HSCT in QuANTUM-First trial and patients who relapsed were censored at the date of relapse. It is worth noting that one of the uncertainties of this exploratory scenario analysis is that the population used to conduct the unanchored MAIC is different from the population in the company base case. In the company base case, to enable a meaningful comparison of the survival outcomes between quizartinib and midostaurin, the QuANTUM-First patient population is reweighted to match with the RATIFY population. Similarly, to enable a meaningful comparison between quizartinib and sorafenib, as described in the responses to question A9c, the QuANTUM-First patient population is reweighted to match with the SORMAIN population.

In the absence of comparative efficacy estimates, this scenario assumes an equivalent post-HSCT relapse for quizartinib and sorafenib. This scenario also included the costs of sorafenib maintenance treatment for both the midostaurin and SC arm.

The result of this exploratory scenario is presented in Table 8. Compared with the company revised base case (Table 7), the ICERs were both slightly improved when comparing with midostaurin (£3,459/QALY gained vs £3,117/QALY gained) and SC (£17,364/QALY gained vs £17,161/QALY gained).

Table 8. Exploratory scenario analysis 1 supporting B9 – applying unanchored MAIC results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,117
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£17,161

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

However, as described in the responses to question A9c, the unanchored MAIC resulted in indicating an xxxxxxxxxxxx xxxxxxxxx xxxxxxx xx xxxxxxxxx xxxx xxxxxxxxxx, xxxx xxxx xxx xxxxxxxxxx xxxxxxxxxx xxxxxxxxx. Landmark survival at xx months was xx.x% in the weighted quizartinib arm as well as the sorafenib arm; the HR was x.xx (95% CI: x.xx, x.xx). Thus, an additional scenario was explored, where it was assumed that sorafenib as the post-HSCT maintenance treatment has the same survival efficacy as quizartinib (i.e., HR=1).

The result of this exploratory scenario is presented in Table 9. Similarly to the first scenario analysis, compared with the base case, the ICERs were both slightly improved when comparing with midostaurin (£3,459/QALY gained vs £3,048/QALY) and SC (£17,364/QALY gained vs £16,941/QALY).

Table 9. Exploratory scenario analysis 1 supporting B9 – assuming same efficacy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER quizartinib vs. (£/QALY)
Quizartinib regimen	£xxx,xxx	x.xx	x.xx	-	-	-	-
Midostaurin regimen	£xxx,xxx	x.xx	x.xx	£x,xxx	x.xx	x.xx	£3,048
SC regimen	£xxx,xxx	x.xx	x.xx	£xx,xxx	x.xx	x.xx	£16,941

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SC, standard chemotherapy.
Notes: These results are the results using the quizartinib PAS price

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Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Clarification questions part 2

May 2024

File name	Version	Contains confidential information	Date
Quizartinib EAG clarification questions	**1.0**	**Yes**	**22/05/2024**

Section A: Clarification on effectiveness data

A5. In response to Question A5, the company provided the HR and 95% CI for CIR in patients with CR during induction for the QuANTUM-First population < 60; i.e., the unadjusted HR used within the MAIC (CS, Table 29).

This is not the correct analysis. Question A5 requested the HR and the 95% CI for CIR in patients with CR during induction for the QuANTUM-First ITT population (i.e, all randomised patients aged 18-75 years represented in CS, Figure 14). Can the company please provide the correct information?

A5 Response: The hazard ratio (HR) and the 95% confidence interval (CI) for cumulative incidence of relapse (CIR) in patients with complete remission (CR) during induction for the QuANTUM-First intention-to-treat (ITT) population are included in Table 1.

Table 1. CIR in patients with CR during induction – quizartinib vs placebo (QuANTUM-First ITT population)

Method	Comparison	HR (95% CI)
QuANTUM-First ITT population	quizartinib vs. placebo	x.xx (x.xx, x.xx)

Abbreviations: CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; HR, hazard ratio; ITT, intention-to-treat.
Source: Daiichi Sankyo DOF, 2024 (1).

A15. In response to Question A15, the company provided the statistical code used for the ML-NMR (Appendix 1). The EAG notes that there may be a typographical error within the code which may have implications for the ML-NMR results.

Pages 115 – 123 describe the ML-NMR analyses for CIR, but the Aggregate Data input from the Rucker at al trial (RATIFY) at the top of page 117 is the HR and 95% CI for OS. Please check and correct this potential error in the code, and provide updated ML-NMR results for CIR.

A15 Response: A more streamlined version of the code can be found in the Appendix 1. Supporting question A15.

Part of the code has been omitted due to its confidential and proprietary nature. It contains intellectual property and includes sensitive data protected by privacy regulations. Enclosed is a summary of the sections that have been omitted, along with the rationale for their removal:

- Sections preparing QuANTUM-First data for analysis have been removed due to their association with the sensitive QuANTUM-First individual patient-level (IPD).
- Sections involving the creation of plots and the execution of diagnostics have been eliminated. These have no impact on the results of the analysis and are subject to intellectual property considerations.
- In circumstances where a choice of approach or model was required, we have removed the code corresponding to the unused approach in the analysis submitted, to preclude any potential confusion.

The code provide should give the EAG the means to conduct appropriate inspection of the executed programme.

The company can confirm that the Aggregate Data input (specifically, HR and 95% CI) from the Rucker et al. trial has been accurately incorporated into the ML-NMR analysis.

Section B: Clarification on cost-effectiveness data

B12. The company appears to have misunderstood the EAG's concerns regarding time on treatment and has not provided the information we require.

There are generally two alternative (and equally valid) approaches that can be used to model time on treatment:

- Use state occupancy to determine discontinuations e.g. patients moving to a progressed disease health state might be assumed to discontinue first-line treatment
- Use time on treatment curves where time on treatment is determined independently of state occupancy.

The EAG is concerned that the company's approach to modelling time on treatment combines both these approaches simultaneously. This may be appropriate but only if the time on treatment data used is appropriately adjusted to avoid double counting discontinuations associated with health state transitions. The requests made in parts b, c and d of question B12 intended to request the data necessary to reconfigure the time on treatment calculations to account for the health state transitions. Could the

company please respond to the following revised set of questions. These will help us better understand if the current calculations are correct and allow us to implement appropriate corrections.

Response B12: Please note the following details about the time-on-treatment analyses provided for questions B12a-d:

- The default population for the time-on-treatment analyses provided for question B12a-d is the company base case population modelled in the CEM. This is the adjusted QuANTUM-First population aligned with the MAIC population (i.e., RATIFY-like population). An alternative analysis for the QuANTUM-First ITT population was also provided in a 'further analysis'. Please find it in B12a continued – Further analysis.
- It was assumed that in the EAG request, when referring to maintenance with and without HSCT, is referring to 'any' HSCT, as 'protocol-specified HSCT' is not mentioned.
- Consideration for off-treatment days within treatment cycles is only given in the supplied 'further analysis'. This is particularly relevant to the induction and consolidation phases. The requested K-M estimates do not adjust for off-treatment days within cycles, when quizartinib is not administered.
- Whilst we have supplied a comprehensive set of additional analyses supporting the EAG's request, the company's method of estimating the quizartinib acquisition cost, (I.e., the health state occupancy approach) allows for any changes made in the model relating to population and proportion receiving HSCT. Whilst there is arguably a degree of discontinuation double counting in the maintenance phase treatment caps (xx.xx months without HSCT; xx.xx months with HSCT) due to the use of mean treatment times, these parameters have been tested in a validation exercise using non-restricted mean survival (exposure time to quizartinib). The modelled equivalent was very close to the empirical value (as presented in responses to question B12 in clarification Part 1).

a) Please provide (uncensored) KM for time on treatment by stage of treatment (induction, consolidation, maintenance without HSCT and maintenance with HSCT). For each stage, time zero should be the beginning of that stage of

treatment and the KM curves should only consider treatment administered within that stage.

Response to B12a: The Kaplan-Meier (K-M) curve for the duration of treatment in the induction phase is provided in Figure 1. All patients who remained on treatment at the end of the induction phase are censored at the last day of induction. Figures 2, 3, and 4 show an alternative with no censoring but with discontinuation at the end of induction considered as an event. A statistical summary and K-M estimates have been uploaded for this uncensored analysis in a separate file.

Figure 1. Time on treatment Kaplan-Meier curve in induction phase censored at last day of induction

Figure 2. Time on treatment Kaplan-Meier curve in induction phase, without censoring

Figure 3. Time on treatment Kaplan-Meier curve in induction phase cycle 1 only, without censoring

Figure 4. Time on treatment Kaplan-Meier curve in induction phase cycle 2 only, without censoring

The K-M curve for the duration of treatment in the consolidation phase is provided in Figure 5. Time zero is the start of consolidation cycle 1. All patients who remained on treatment at the end of the consolidation phase are censored at the last day of consolidation. Figure 6 shows an alternative with no censoring but with discontinuation at the end of the consolidation phase considered as an event. A statistical summary and K-M estimates have been uploaded for this uncensored analysis in a separate file.

Figure 5. Time on treatment Kaplan-Meier curve in consolidation phase censored at the last day of consolidation

Figure 6. Time on treatment Kaplan-Meier curve in consolidation phase, without censoring

The K-M curve for the duration of treatment for patients who were in the maintenance phase without HSCT is provided in Figure 7. All patients who did not discontinue at the end of maintenance are censored at the last date of maintenance. Figure 8 shows an alternative with no censoring but with discontinuation at the end of the maintenance phase considered as an event. A statistical summary and K-M estimates have been uploaded for this uncensored analysis in a separate file.

Figure 7. Time on treatment Kaplan-Meier curve treatment in the maintenance phase for patients without HSCT censored at the last date of maintenance

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

Figure 8. Time on treatment Kaplan-Meier curve treatment in the maintenance phase for patients without HSCT, without censoring

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

The K-M curve for the duration of treatment for patients who were in the maintenance phase with HSCT is provided in Figure 9. All patients who did not discontinue at the end of maintenance are censored at the last date of maintenance. Figure 10 shows an alternative with no censoring but with discontinuation at the end of maintenance considered as an event. A statistical summary and K-M estimates have been uploaded for this uncensored analysis in a separate file.

Figure 9. Time on treatment Kaplan-Meier curve treatment in the maintenance phase for patients with HSCT censored at the last date of maintenance

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

Figure 10. Time on treatment Kaplan-Meier curve treatment in the maintenance phase for patients with HSCT, without censoring

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

B12a continued – Further analysis

A third approach to the question/request is provided in this section. To further support the EAGs request, we present a duration of treatment analysis by treatment phase for the QuANTUM-First ITT analysis set. These analyses include adjustments for days off-treatment, such as induction cycle days 1 to 7 and 22 to 28. Please note that the KM estimates are not censored.

Figure 11 presents duration of treatment for the (up to) two cycles of induction therapy, accounting for off-treatment days. Quizartinib is administered only on days 8-14 of the treatment cycle during this phase.

Figure 11. Adjusted duration of treatment in Induction phase – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Figure 12 presents duration of treatment for the (up to) four cycles of consolidation therapy for those attaining remission (as per study protocol). Quizartinib was administered once per day on days 6-19 of the treatment cycle during this phase.

Figure 12. Adjusted duration of treatment in Consolidation phase – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Figure 13 presents the duration of treatment during the maintenance phase for all patients entering continuation.

Figure 13. Adjusted duration of treatment in Maintenance phase (all) – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Figure 14 presents the subset who do not subsequently receive a protocol-specified HSCT (either have no HSCT or non-protocol-specified HSCT)

Figure 14. Adjusted duration of treatment in Maintenance phase (without protocol-specified HSCT) – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Figure 15 presents the remaining subset who subsequently receive protocol-specified HSCT.

Figure 15. Adjusted duration of treatment in Maintenance phase (with protocol-specified HSCT) – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Question B12 part b)

b) or the consolidation phase (only), please provide KM data for time on treatment censored for relapse, HSCT and death events. As above, time zero should be the beginning of that stage of treatment and only consider treatment administered within that stage.

Response to B12b: The requested KM curve is presented in Figure 16.

Figure 16. Time on treatment Kaplan-Meier curve, censored for relapse, HSCT, and death (consolidation phase only)

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

c) For the maintenance phase (only) in patients who do not proceed to HSCT, please provide KM data for time on treatment censored for relapse and OS. As above, time zero should be the beginning of that stage of treatment and only consider treatment administered within that stage.

Response to B12c: The requested KM curve is presented in Figure 17.

Figure 17. Time on treatment Kaplan-Meier curve in patients who without HSCT, censored for relapse and death (maintenance phase only)

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

d) For the maintenance phase (only) in patients who proceed to HSCT, please provide KM data for time on treatment censored for relapse and OS. As above, time zero should be the beginning of that stage of treatment and only consider treatment administered within that stage.

Response to B12d: The requested KM curve is presented in Figure 18.

Figure 18. Time on treatment Kaplan-Meier curve in patients who with HSCT, censored for relapse and death (maintenance phase only)

Abbreviation: HSCT, allogeneic haematopoietic stem cell transplantation.

e) By stage of treatment, please provide reasons for discontinuation.

Response to B12e: The reasons for discontinuation by treatment phase in the QuANTUM-First as provided in the Table 2. The data presented is derived from the QuANTUM-First Safety Analysis Set, as opposed to the weighted population utilized in the MAIC (i.e. RATIFY-like population).

Table 2. Subject Disposition in the QuANTUM-First - Reasons for Discontinuation by Treatment Phase (Safety Analysis Set)

	Quizartinib (N=265)	Placebo (N=268)	Total (N=533)
	n (%)	n (%)	n (%)
Entered Induction Phase	**265 (100.0)**	**268 (100.0)**	**533 (100.0)**
Discontinued Study Treatment from Induction Phase	92 (34.7)	93 (34.7)	185 (34.7)
Primary Reason for Discontinuation from Induction Phase[a]			
Adverse Event	28 (10.6)	11 (4.1)	39 (7.3)
Death	0	1 (0.4)	1 (0.2)
Refractory Disease	41 (15.5)	70 (26.1)	111 (20.8)
Relapse	2 (0.8)	3 (1.1)	5 (0.9)
Non-Protocol Specified AML Therapy	2 (0.8)	0	2 (0.4)
Investigator Decision	4 (1.5)	2 (0.7)	6 (1.1)
Subject decision to stop study drug	11 (4.2)	6 (2.2)	17 (3.2)
Lost to Follow-up	1 (0.4)	0	1 (0.2)
Other	3 (1.1)	0	3 (0.6)
Entered Consolidation Phase	**173 (65.3)**	**175 (65.3)**	**348 (65.3)**
Discontinued Study Treatment from Consolidation Phase	57 (21.5)	83 (31.0)	140 (26.3)
Primary Reason for Discontinuation from Induction Phase[a]			
Adverse Event	11 (4.2)	5 (1.9)	16 (3.0)
Relapse	19 (7.2)	38 (14.2)	57 (10.7)
Non-Protocol Specified AML Therapy	3 (1.1)	2 (0.7)	5 (0.9)
Investigator Decision	3 (1.1)	4 (1.5)	7 (1.3)
Failure to Meet Continuation Criteria	5 (1.9)	11 (4.1)	16 (3.0)
Subject decision to stop study drug	6 (2.3)	13 (4.9)	19 (3.6)
Other	10 (3.8)	10 (3.7)	20 (3.8)
Entered Maintenance Phase	**116 (43.8)**	**92 (34.3)**	**208 (39.0)**
Discontinued Study Treatment from Continuation Phase	63 (23.8)	43 (16.0)	106 (19.9)
Primary Reason for Discontinuation from Induction Phase[a]			
Adverse Event	19 (7.2)	7 (2.6)	26 (4.9)
Relapse	23 (8.7)	24 (9.0)	47 (8.8)
Non-Protocol Specified AMLTherapy	7 (2.6)	4 (1.5)	11 (2.1)
Pregnancy	0	1 (0.4)	1 (0.2)
Investigator Decision	3 (1.1)	1 (0.4)	4 (0.8)
Failure to Meet Continuation Criteria	0	1 (0.4)	1 (0.2)
Subject decision to stop study drug	8 (3.0)	4 (1.5)	12 (2.3)
Other	3 (1.1)	1 (0.4)	4 (0.8)

Abbreviations: AML, Acute Myeloid Leukaemia.
Note: The primary reasons for discontinuation from study treatment are as follows: Adverse Events, Death, Refractory Disease, Relapse, Non-protocol Specified AML Therapy, Pregnancy, Subject decision to stop study drug, Study terminated by Sponsor, Protocol Violation, Lost to Follow-up, Investigator Decision, Subject does not meet one or more of the eligibility criteria for the Continuation Phase, and Other. If the number of subjects discontinued study treatment due to a reason is greater than 0, the reason and the corresponding number are presented in the table.
Reference: Erba et al. 2023 (2).
Data cut-off date: 13 Aug 2021.

f) Please explain the derivation of the mean time on treatment reported in Table 66 of the company submission. Please confirm if these are restricted mean survival time. If possible, please provide updated values using the latest safety data cut.

Response to B12f: The mean time on treatment for the induction and consolidation phases, reported in Table 66 of the company submission, is sourced from the mean unadjusted treatment duration in the QuANTUM-First trial (DCO August 2021) in the Safety Analysis Set, detailed in Table 3. These are not considered as the restricted means, given no patients remain unfinished in the induction and consolidation phases. The treatment duration (days) for each phase is equal to the last dose date minus the first dose date plus one within each phase. The mean unadjusted treatment durations in the induction phase for the quizartinib and SC arms are x.xx weeks (equivalent to x.xx 28-day drug cycles) and x.xx weeks (equivalent to x.xx drug cycles), respectively. The mean unadjusted treatment durations in the consolidation phase for the quizartinib and SC arms are x.xx weeks (equivalent to x.xx drug cycles) and x.xx weeks (equivalent to x.x drug cycles), respectively.

The adjusted treatment duration (days) for each phase is the treatment duration minus the planned off-drug days in each phase (e.g., the time between the end of induction cycle 1 and the start of induction cycle 2), which is also planned in Table 3. The mean treatment duration of the induction phase decreases from x.xx to x.xx drug cycles (equivalent to x.xx weeks) for the quizartinib arm and decreases from x.xx to x.xx drug cycles (equivalent to x.xx weeks) for the SC arm. The mean treatment duration of the consolidation phase decreases from x.xx to x.xx drug cycles (equivalent to x.xx weeks) for the quizartinib arm and decreases from x.x to x.xx drug cycles (equivalent to x.xx weeks) for the SC arm.

Table 3. Study Drug (Quizartinib/Placebo) Exposure in Induction and Consolidation Period (Safety Analysis Set)

Unadjusted Treatment Duration (weeks)			Adjusted Treatment Duration (weeks)		
	Quizartinib	Placebo		Quizartinib	Placebo
Induction phase					
n	265	268	n	265	268
Mean	x.xx	x.xx	Mean	x.xx	x.xx
SD	x.xx	x.xx	SD	x.xx	x.xx
Median	x	x	Median	x	x
Min, Max	x.x, xx.x	x.x, xx.x	Min, Max	x.x, x.x	x.x, x.x
Consolidation phase					
n	166	169	n	166	169

Unadjusted Treatment Duration (weeks)			Adjusted Treatment Duration (weeks)		
	Quizartinib	Placebo		Quizartinib	Placebo
Mean	x.xx	x.xx	Mean	x.xx	x.xx
SD	x.xx	x.xx	SD	x.xx	x.xx
Median	x	x	Median	x	x
Min, Max	x.x, xx.x	x.x, xx.x	Min, Max	x.x, x.x	x.x, x.x

Abbreviations: DCO, data cut off; HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
Notes: Treatment Duration (days) for each phase = last dose date – first dose date + 1 within each phase. Adjusted Treatment Duration (days) for each phase is the treatment duration minus the planned off drug days in each phase.
Source: Daiichi Sankyo, 2022 (3) (Data cut-off date: 13 Aug 2021).

The mean time on treatment for the maintenance phase for patients with and without HSCT (provided in the initial responses to EAG clarification questions, Table 50) is sourced by an additional internal analysis based on the IPD data from the Safety Analysis Set in the QuANTUM-First trial (Daiichi internal analysis T.5.1.3_EXPO_SAS (1)). The company would like to correct a typo in the title of Table 50. The mean time on treatment for the maintenance phase used in the base case is based on the DCO 13 August 2021, instead of 13 August 2023. Theses mean time on treatment for the maintenance phase are based on restricted mean survival time.

The mean treatment duration by treatment phase was not available for the new DCO 16 June 2023. The treatment duration of all treatment phases results in the new DCO are consistent with the results observed at the initial CSR DCO 13 August 2021 (compared in Table 4). Thus, the difference in the mean treatment duration by treatment phase in the DCO 16 June 2023 compared with the restricted means from the DCO 13 August 2021 was expected to be limited.

Table 4. Summary of Study Drug Exposure (Safety Analysis Set) in DCO (13 Aug 2021) and DCO (16 Jun 2023)

	CSR DCO (13 Aug 2021)		Addendum DCO (16 Jun 2023)	
Category	**Quizartinib (N = 265)**	**Placebo (N = 268)**	**Quizartinib (N = 265)**	**Placebo (N = 268)**
Treatment duration[a] (weeks)				
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (min, max)	xx.xx (x.x, xxx.x)	x.xx (x.x, xxx.x)	xx.xx (x.x, xxx.x)	x.xx (x.x, xxx.x)
Total subject-years of exposure	xxx.xx	xxx.xx	xxx.xx	xxx.xx

Abbreviations: CSR, clinical study report; DCO, data cut-off; max, maximum; min, minimum; N, total number of subjects; SD, standard deviation.
Notes: a Treatment duration (weeks) = (date of last dose - date of first dose + 1)/7.

Reference

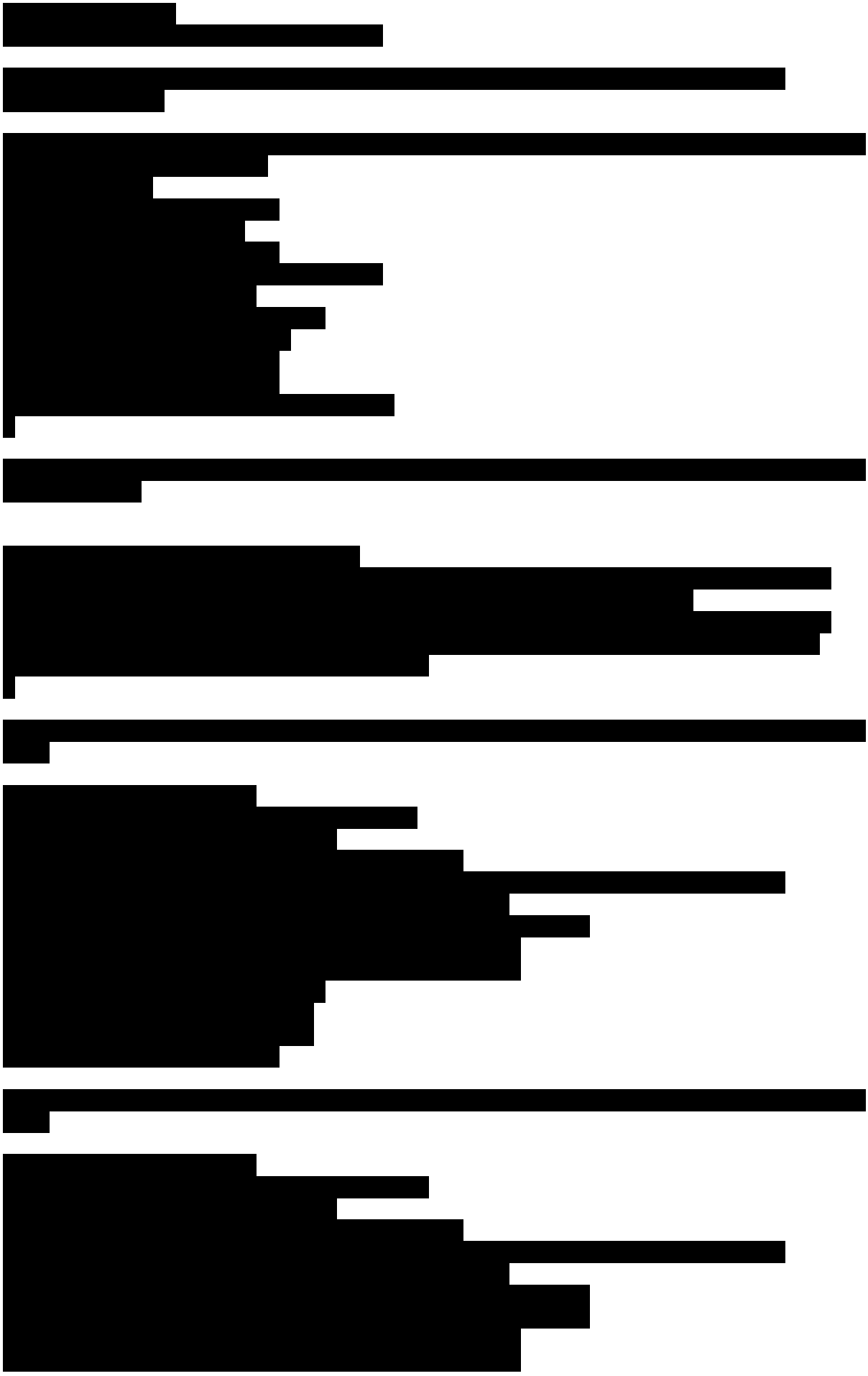
1. Daiichi Sankyo Inc. Post-hoc analysis [DOF]. 2024.

2. Erba HP, Montesinos P, Kim HJ, Patkowska E, Vrhovac R, Zak P, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10388):1571-83.

3. Daiichi Sankyo Inc. QuANTUM-First clinical study report. Version 2.0. 2022.

Appendix 1. Supporting question A15

[redacted]



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Clarification questions part 2

May 2024

File name	Version	Contains confidential information	Date
Quizartinib EAG clarification questions	**1.0**	**Yes**	**23/05/2024**

Section B: Clarification on cost-effectiveness data

B12. The company appears to have misunderstood the EAG's concerns regarding time on treatment and has not provided the information we require.

There are generally two alternative (and equally valid) approaches that can be used to model time on treatment:

- Use state occupancy to determine discontinuations e.g. patients moving to a progressed disease health state might be assumed to discontinue first-line treatment

- Use time on treatment curves where time on treatment is determined independently of state occupancy.

The EAG is concerned that the company's approach to modelling time on treatment combines both these approaches simultaneously. This may be appropriate but only if the time on treatment data used is appropriately adjusted to avoid double counting discontinuations associated with health state transitions. The requests made in parts b, c and d of question B12 intended to request the data necessary to reconfigure the time on treatment calculations to account for the health state transitions. Could the company please respond to the following revised set of questions. These will help us better understand if the current calculations are correct and allow us to implement appropriate corrections.

a) Please provide (uncensored) KM for time on treatment by stage of treatment (induction, consolidation, maintenance without HSCT and maintenance with HSCT). For each stage, time zero should be the beginning of that stage of treatment and the KM curves should only consider treatment administered within that stage.

B12a continued – Further analysis - 2

A third approach to the question/request is provided in this section. To further support the EAGs request, we present a duration of treatment analysis by treatment phase for the QuANTUM-First ITT analysis set. These analyses include adjustments for days off-treatment.

These two additional figures supplement the further analysis of the original response for B12a in clarification part 2 (supplied separately) and consider an alternative division of the maintenance period (1).

Figure 1 presents the maintenance subset who do not subsequently receive any HSCT. Figure 2 presents the remaining subset who do subsequently receive any HSCT (protocol-specified or non-protocol-specified HSCT).

Figure 1. Adjusted duration of treatment in Maintenance phase (without any HSCT) – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Figure 2. Adjusted duration of treatment in Maintenance phase (with any HSCT) – Time-to-event-analysis-DCO 13-Aug-2021-ITT set

Reference

1. Daiichi Sankyo Inc. Post-hoc analysis [DOF]. 2024.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Blood Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Blood Cancer UK is the UK's biggest blood cancer research charity. We fund research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has ~120 employees and is funded primarily through donations and legacies.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We received £35,000 for the Blood Cancer Action Plan from BMS.
4c. Do you have any direct or indirect links	None

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information for this appraisal was gathered from insights derived through our communications with the clinical and patient community, particularly those personally affected by acute myeloid leukaemia including patients themselves and their loved ones who care for them. Blood cancer UK has close relationships and maintains regular contact with the haemato-oncology community. We do this through our Healthcare Professional Advisory Panel (HPAP), Nurses Working Group (NWG), our patient ambassador network etc. We additionally maintain relationships with many other blood cancer specialists – from research nurses to academic researchers – through our Information and Support, Research, and Policy, Campaigns and Engagement teams. We specifically reached the patient group of interest for this appraisal through our social media channels and our clinical networks who put us in touch with patients willing to share their experiences with us including an individual with the FLT3 mutation. We also directly reached out to our patient community who responded with a willingness to share their experiences. We have also included information based on our previous conversations with people who have acute leukaemia. These conversations built our understanding of the experiences of those affected by the issues of interest for this appraisal.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	On average, more than 3,000 new cases of acute myeloid leukaemia (AML) are diagnosed each year in the UK. AML is one of the most aggressive types of blood cancer with some of the worst outcomes in terms of survival. The disease progresses quickly and if left untreated, can be fatal. People diagnosed with AML experience a variety of symptoms including anaemia, recurrent infections, bone pain, headaches etc. Depending on the extent of anaemia, people affected can also experience fatigue, shortness of breath and generalised weakness. In addition to this, patients with FLT3 mutations are told their prognosis is even worse because of the mutation. One patient explained how immediately after receiving a diagnosis, she was 'very aware that AML was a killer.' Treatment needs to start so quickly; many patients have no chance to prepare practically or emotionally. Often people are rushed to hospital, diagnosed, and start chemotherapy in a matter of days. The overarching impact is one of complete shock and fear for their life, justifiably. Most people will spend many months in hospital, having highly intensive treatments that cause extremely debilitating and painful side effects. The vast majority cannot work or even be at home for long periods of time, with significant effects on their finances and family including any partners or children. It is common for people with AML to have repeated infections which can quickly become life-threatening or develop into sepsis. One individual stated how it is 'easy for others not to realise the gravity of infections for AML.' Patients describe AML as extremely frightening, a rollercoaster, stressful, and without any stability of what may happen next. Our conversations with people affected by AML have highlighted that it is normal to have regular setbacks or to find out that treatment is not working. Living in fear of AML has many implications including psychological ones which are eased by the knowledge and hope of new research and treatments becoming available. For family and carers, seeing their loved one deteriorate before their eyes is one of the most challenging aspects. Weight loss and side effects build up quickly during treatment and patients as well as carers say that the person in front of them isn't someone they recognise. It is an extremely debilitating illness and treatment, and recovery take a long time. Patients are often left with long-term effects many years after treatment, like chronic fatigue, ongoing susceptibility to infections, heart damage and secondary cancers.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients have acknowledged that the current treatment options available on the NHS do not work for everybody and are very harsh on their bodies. One patient explained 'people die from their treatments, and I'm not surprised.' Another individual described being informed by their clinical team of the possible side effects before starting chemotherapy and was shocked at how she experienced 'every single one' that was explained to her. The current treatments have been described as very aggressive, 'beyond your imagination' and 'so damaging to other parts of the body.' One person explained 'I had skin rashes, diarrhoea, mouth ulcers. I became incontinent, my nails started splitting, I lost my hair, I was spitting out gum tissue, got sepsis twice. It was really really grim.' We spoke to another patient who suffered from mild to moderate heart damage following treatment and therefore could not continue with their planned treatment course. One patient described they spent the first 5 weeks in hospital and then received the chemo cycles as an outpatient but was frequently admitted back into hospital for periods due to serious infections and side effects. They experienced hair loss, muscle wastage, extreme weakness and weight loss going from 'a healthy size 12 to a size 6'. They spent a significant amount of time in bed for the first 6 months of treatment which was very hard on them. Although a lot of patients experience extensive side effects during and after treatment, the battle is not over for them as many suffer relapses. One patient described 'I feared relapse like nothing else' for many years.
8. Is there an unmet need for patients with this condition?	The current treatment landscape for newly diagnosed FLT-3 ITD-mutated AML in the UK has its limitations. Although midostaurin is a FLT-3 inhibitor, there is still no treatment which specifically targets the ITD mutation like Quizartinib does. Furthermore, with the current treatment options, patients still face poor outcomes and a high chance of relapse. Today patients and families have hope that newer, more targeted treatments can truly improve relapse-free survival and reduce the debilitating long-term effects of more toxic treatments. Newly diagnosed patients, particularly those with a FLT3 mutation, desperately need new treatment options so they can get into remission and continue on to recovery. Currently, FLT3-ITD positive patients are acutely aware that the odds are stacked against them, but having more options for more targeted treatments could change this. Considering the frequency of FLT-3 mutations within AML and the poor prognosis associated with ITD mutations in particular, Quizartinib offers a highly selective and a potentially effective option to manage patients with these mutations.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	New therapies that offer an alternative treatment option are always welcome by patients and their loved ones. This is especially true if they have the potential to provide a survival benefit, as is the case with quizartinib if added to standard chemotherapy treatment. Quizartinib's oral administration is an advantage for people affected. Patients generally prefer oral treatment to IV infusion due to a number of factors including convenience. This will also mean it's easier for patients to continue the treatment during maintenance phase in the comfort of their home. Additionally, as quizartinib only needs to be taken once a day, patients may prefer this over other treatments which may need to be taken more than once a day, like midostaurin. This dosing schedule and its oral method of administration causes minimal disruption to patients and their carers day to day lives whilst retaining the clinical benefits it can provide. Quizartinib's selectivity and potency are also an advantage.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with any treatments, the potential side effects and managing toxicities can be a challenge for patients and carers. As older patients are more susceptible to serious infections, they may require additional monitoring which may add additional interference to their lives. However, this monitoring may also help to provide reassurance for them and their loved ones. For patients who are considering having children in the future, the potential for treatments such as Quizartinib to interfere with their fertility can be a disadvantage.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	When considering the survival benefit, younger individuals who receive quizartinib may potentially benefit more from the treatment than those who are older and so may be frailer, and therefore, less able to tolerate intensive treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• AML is a very aggressive, debilitating, and fast-progressing disease. People are rushed into treatment soon after diagnosis without having the time to prepare. They then live with the challenges associated with the disease itself coupled with the extensive side effects from intensive treatments which can cause long-term effects. • An AML diagnosis can evoke heightened feelings of anxiety, fear, uncertainty, and decreased ability to resume social and familial roles. This has damaging impacts on their mental and physical health. • There's currently an unmet need for those with FLT3-ITD-mutated AML as no treatments specifically target the ITD mutation (which is associated with a worse prognosis out of the two FLT-3 mutations). • Incorporating quizartinib, a targeted treatment option, into the standard treatment plan is a significant step forward for this subset of patients with FLT3-ITD -mutated AML as it can provide a survival benefit and improve quality of life. Quizartinib is generally a well-tolerated treatment. It is an oral tablet which is convenient for many patients. • The clinical benefits of quizartinib (its potential to improve survival and outcomes) are welcome by patients and carers. Quizartinib also has the potential to benefit older patients which is relevant as the median age of diagnosis is above 60 years of age where outcomes have historically been bleak.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected by leukaemia, MDS or MPNs receives the best possible diagnosis, information, advice, treatment and support. Approximately 80% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 20% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	**Celgene** - £65,000 patient activities of which £15,000 is for the Blood Cancer Alliance **Jazz** - £30,000 awareness and patient support **Novartis** - £25,000 core funding, £25,000 for videos, podcasts and webinars and £487 honorarium **Pfizer** - £10,000 core funding

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information for this submission gathered through the Leukaemia Care patient experience survey – 'Living with Leukaemia'. The latest survey, run in 2017, had 2884 responses (including 443 AML patients). We also gathered statistics from a 2021 survey of AML patients regarding their views on treatment. We spoke to an AML patient in September 2023 to understand their views on unmet needs and the impact of an AML diagnosis. This is reflected as quotes in this submission. We also spoke to another AML patient in 2021 regarding their experience of AML and treatment options, also reflected as quotes in the submission. Additionally, we have gathered further information through our online forums, helpline, support groups, and communication with our membership. We also sought advice from clinical advisors via one-to-one conversations. We were not able to speak directly with any patient who had experience of quizartinib, despite efforts to do so.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute myeloid leukaemia (AML) accounts for around a third of cases of leukaemia in adults in the UK. There are around 3,100 new acute myeloid leukaemia cases in the UK every year, that's more than 8 every day (2016-2018). Approximately two thirds of patients in the UK are diagnosed aged 65 and over; with the highest incidence rates in people aged 85-89 in the UK (2016-2018). Older age is associated with poorer prognosis; however, AML is an aggressive leukaemia and can affect people of any age. Due to the rapidly progressing nature of AML, 54% of patients in our Living with Leukaemia survey said they had experienced symptoms for less than a month before visiting their GP. The most common symptoms encountered by AML patients since their diagnosis are fatigue (73%), feeling weak or breathless (51%), memory loss or loss of concentration (38%), bleeding and bruising (37%), itchy skin (35%), nausea or vomiting (35%), sleeping problems (34%), infections (32%), bone or joint pain (31%), weight loss (28%) and muscle pain (23%). The National Cancer Intelligence Network 'Routes to Diagnosis' report shows that 53% of AML patients are diagnosed via emergency presentation, compared to a cancer average of 22%, and emergency diagnosis is correlated with poor prognosis. Patients with acute leukaemia often get ill suddenly and must start treatment quickly; 55% of AML patients surveyed started treatment within a week of diagnosis. AML also has a wider practical impact, with 52% of patients experiencing pain as a direct result of their condition (31% occasionally, 17% regularly and 4% constantly). Additionally, 51% of patients have difficulty moving around (sometimes 27%, often 15% and always 9%) and 69% of AML patients have difficulty performing some of their daily routines, such as cooking or cleaning. Another 38% reported that they have problems taking care of themselves. AML patients can also experience a considerable emotional impact as a result of their diagnosis, prompting them and their families to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. Our survey reports 51% of AML patients have felt depressed or anxious more often since their diagnosis.

	77% of those in work or education experienced a negative impact on this post diagnosis (32% reduced hours, 45% no longer able to work or continue education). Consequently, 53% of AML patients reported a negative financial impact as a result of having cancer (increased costs or reduced income). This financial impact can have a ripple effect on family members and can also be particularly devastating when in those with a reduced income already, such for those who are retired. An AML patient we spoke to previously describes her experience of diagnosis on herself and those around her. She said *"the shock and upheaval was enormous and very disorientating. I have two young boys, my husband runs his own business and I am a singing teacher. We had to make immediate arrangements to cover childcare and work appointments and then look at how to sustain this for the coming months. The impact of a disease like this ripples through your immediate family and into your network of friends and colleagues."* The physical, financial and emotional impact of AML does not affect the patient in isolation and is often also felt by carers and family members. According to an international survey run by the Acute Leukaemia Advocates Network in 2019, 35% of patients reported their AML definitely had an emotional impact on their family, friends or carers. As such, improvements in a patient's treatment options and prognosis will have a wider impact on the lives of their family and friends. Another AML patient we spoke to this year (2023), said: *"The diagnosis of AML had a massive impact on me and my family - particularly as this occurred during the Covid pandemic. The illness and treatment alone had a significant effect on my physical health, going almost overnight from a 'normal' healthy active person - to struggling to get upstairs and needing to sleep during the day or after any small physical exertion due to extreme fatigue. However, I found the emotional impact of AML more significant and traumatic than the physical aspect - life was suddenly turned upside down - I didn't know if I would survive the illness; my kids were young so didn't understand the diagnosis and I was isolated from my family for long periods of time. It took a long time to process what had actually happened and how I could move on."*

	If patients are unable to care for themselves, these family and friends can then become carers. Many patients (41% of those surveyed) feel their AML has had an impact, to some extent, on the social activities of their family, friends or carers, this is likely due to increased responsibilities. This can be a huge change in dynamics in the relationship between the patients and their relative/friend, with emotional effects. Additionally, caring is physically exhausting and may be done in addition to paid work. Alternatively, family may have to give up work to care for the patients, leaving the family in even more financial difficulty.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	In a 2021 survey Leukaemia Care conducted with AML patients, when asked if they thought existing treatment options for AML on the NHS were sufficient 77.8% of respondents said either no or not sure. Although there is another maintenance treatment now approved in the time since the survey, We believe many patients would still like to see more effective therapies in this setting. Chemotherapy is used in both induction and consolidation therapy for AML and can also be used in maintenance therapy in the form of salvage chemotherapy. Chemotherapy is an intensive treatment associated with severe side effects as reported by patients. One AML patient reports, "*I was given standard chemotherapy. I suffered various side effects from rashes, high fevers of 41.7, sepsis, erythema nodosum, lung fungal infections and the usual vomiting and diarrhoea. I also suffered an excruciating inflammation of the small intestine*". In the maintenance setting, some patients will be eligible and decide to go on and receive a stem cell transplant. For the group who are eligible and decide to receive a stem cell transplant, the options are then limited if this is unsuccessful or thought likely to be unsuccessful. They cannot be treated with midostaurin or oral azacitidine as these are only suitable for those who will not go on to receive a stem cell transplant. Salvage chemotherapy can also be used in the maintenance setting, but this only extends patient lives by a matter of months.

Commented [A1]: This is the most up to date version of this stat but is it too outdated to be relevant? Oral azacitidine as maintenance has been approved in the setting since then.

Commented [A2]: My understanding from speaking to Steve is that quizartinib can be used before/after SCT but midostaurin and oral azacitidine can't be. So I am setting the scene for the need for a treatment which can do that and will write that quizartinib can in the advantqages section. I haven't been able to fully verify this though (other than conversation with Steve)

Commented [A3]: We are missing what people's thoughts are on midostaurin. This could be useful if we have this info anywhere as it's the biggest comparator here and there aren't any head to head trials comparing quizartinib with midostaurin, so it will be hard for NICE to show it's benefit.

8. Is there an unmet need for patients with this condition?	There is currently only one targeted treatment option available to patients with the FLT3 mutation, namely the first generation TKI midostaurin. We know that patients and clinicians alike value having as many treatment options as possible, including treatments with different characteristics/modes of action. This is so clinicians can tailor and personalize treatment plans to find the best treatment for the individual patient. What works for one patient, will not always work well for another. The unmet need for increased treatment options is especially important in this setting as people with the FLT3 mutation have lower chance of achieving remission and shorter overall survival than AML patients without the mutation. There is also an unmet need for treatments which have reduced adverse side effect profiles as this can have a direct impact on the patient's quality of life. An AML patient we spoke to in 2023 said "*different treatments may have a range of differing side effects which will also impact on a patient's quality of life, so having options for treatment allows patients to choose the most suitable treatment for them (in conjunction with their healthcare team).*" The unmet need for more options applies across all indications being reviewed (induction, consolidation and maintenance).

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Quizartinib is a targeted treatment, targeting the FLT3 mutation in AML. Patients with this mutation have worse prognosis, so a drug designed to inhibit the mutated cells could prove to be effective for this group. The comparator midostaurin is a 1st generation TKI, whereas quizaritinib is a 2nd generation TKI. There is little research comparing the efficacy of 1st and 2nd generation TKIs, but as the 2nd generation is more targeted than the first, it is predicted to have fewer adverse events, which would be an advantage for patients. In the maintenance treatment setting, unlike oral azacitidine and midostaurin, quizartinib can be used before a stem cell transplant. This is a clear benefit of quizartinib, which addresses a current unmet need in this population. In addition, quizartinib is an oral treatment, which is a convenient and often preferred method of treatment for patients. When comparing to other methods of treatment, like intravenous, an AML patient told us *"having a drug orally would have made a major difference as it would have freed up a significant part of my time and enabled me to lead a much more 'normal' life."* Finally, in a pre-clinical study in 2020, there was evidence to suggest the potential value of quizartinib to demonstrate antileukaemic activity in patients who are resistant to midostaurin (Aikawa T, Togashi N, Iwanaga K, et al.).

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As mentioned above, research into 2nd generation TKIs compared 1st generation TKIs is still ongoing. However, it could be show to be the case that a more targeted inhibitor like a 2nd gen TKI such as quizartinib is not as effective as a 1st generation inhibitor, as there are many mutations in AML and a 1st gen TKI targets all tyrosines. Quizartinib has also been shown to have adverse events of ECG changes and QT prolongation, but clinicians report that these can often be dose dependent and are therefore easily mitigated by lowering the dose.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There is unmet need still for patients who are having any type of treatment, as current maintenance options are limited by your eligibility for other treatments. More freedom to treat would be welcome for many patients.

Commented [A4]: Don't want to narrow the scope, but potentially as maintenance treatment in those who are eligible to receive a SCT (as quizartinib addresses an unmet need there that other treatments don't).

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Survival for AML remains poor and it can have significant impacts on quality of life. • Research has shown relapse to be a particularly difficult time for patients and preventing this would improve their quality of life. • Quizartinib could help improve survival for this group of patients in whom the risk of relapse is higher, thanks to the FLT3 mutations. • Side effects found in the trials are manageable by healthcare professionals • Patients are likely to welcome this treatment as an option for an illness that is difficult to treat with current conditions.

Thank you for your time.

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Professional organisation submission

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologist and the University of Dundee/NHS Tayside
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to enhance survival in patients with previously untreated acute myeloid leukaemia (AML) with internal tandem duplication in the fms-related tyrosine kinase 3 (*FLT3*) gene (*FLT3*-ITD).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In this patient group, key clinical responses are defined by a reduction in relapse, prolongation of survival (potentially leading to cure), and the maintenance of an acceptable toxicity profile.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, despite recent advances, there continues to be an unmet need for a significant proportion of patients, as long-term survival in individuals with this particular sub-type of AML is ~50% with current intensive standard-of-care treatment (relevant to this submission).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently, non-trial patients with previously untreated *FLT3*-ITD AML (without core-binding factor re-arrangements, therapy-related AML, a history or karyotype suggestive of antecedent haematological disorder), deemed eligible for intensive chemotherapy, begin induction treatment with daunorubicin, cytarabine (DA) and midostaurin (DA+midostaurin), if *FLT3* gene analysis results are available around the time of treatment initiation. In cases where *FLT3* results are unavailable, induction treatment with DA and the anti-CD33 immunoconjugate gemtuzumab ozogamicin (GO) may be initiated, with the 'off licence' addition of midostaurin on completion of

	chemotherapy, or during subsequent treatment cycles. A smaller subset of patients may undergo induction treatment with an intensified chemotherapy schedule (FLAG-Ida-GO). While the incorporation of higher doses of daunorubicin in DA may benefit patients with *FLT3* mutant AML, this is not standard practice. Patients with core-binding factor re-arrangements, should the result be available at the start of treatment, are more likely to be treated with DA + GO, and those with therapy-related or secondary AML with a *FLT3*-ITD may receive DA+midostaurin or Vyxeos. Outside clinical trials, patients considered unsuitable for intensive chemotherapy receive lower-intensity therapy with venetoclax and azacitidine (ven_aza), with a smaller proportion receiving venetoclax and low-dose cytarabine (LDAC), or monotherapy with azacitidine or LDAC. Patients ineligible for disease-modifying therapies receive exclusive supportive care, unaffected by this submission. Responders to disease-modifying therapy are considered for allogeneic stem cell transplantation (alloSCT) in first complete remission, should they fulfil eligibility for an allograft. In the United Kingdom, this generally applies to patients who have received intensive treatment. If alloSCT is not considered, intensively treated patients receive maintenance treatment with midostaurin. and if not tolerated, oral azacitidine. In alloSCT recipients, maintenance treatment with Sorafenib is also a consideration.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Clinical management guidelines from North America (NCCN), Europe (ESMO) and a 'good practice paper' from the British Society of Haematology are sources of information to guide treatment. Additionally, web-based applications ('app') can also be used as a guide.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In my Scotland-based experience, there is consensus across the NHS within the United Kingdom in many areas of the pathway of care. For example, there is agreement in the choice of induction therapy for a patient with de novo, normal karyotype AML, eligible for intensive therapy, in whom a *FLT3* variant is identified at the time of treatment. These patients typically receive DA + midostaurin. However, more contentious decisions arise in cases with overlapping diagnostic and clinicopathological information, for example, AML patients with both a *FLT3* variant and a history of myelodysplastic syndrome (MDS), or MDS-related cytogenetic abnormalities. Differences of opinion in these cases can be attributed to variations in the interpretation of sub-group analysis in different trials, which, based on small numbers is subject to bias. Additionally, differences in practice may stem from interpretation of emerging clinical trial data. For example, UK clinical trial data suggest numerical superiority in survival with FLAG-Ida + GO in a sub-group of patients with *FLT3* mutant disease over the current standard (DA + midostaurin), even if the data are derived from different clinical trials.
9c. What impact would the technology have on the current pathway of care?	The introduction of new technology (drug) offers another treatment option for physicians and patients with previously untreated AML with *FLT3*-ITD.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology (drug) will be employed in a similar manner to the current standard of care (DA + midostaurin) up to the point of alloSCT. There are notable differences: 1. only patients with *FLT3*-ITD are eligible for treatment with quizartinib in contrast to the broader eligibility for midostaurin, that includes patients with *FLT3*-ITD and tyrosine kinase domain (TKD) mutations. 2. Maintenance with quizartinib can be resumed following allo SCT unlike in current NHS practice where midostaurin or oral azacitidine may not be routinely used in the post-transplant setting. 3. The number of cycles of maintenance therapy is 36 compared to 12 cycles of midostaurin.
10a. How does healthcare resource use differ between the technology and current care?	The duration of therapy with quizartinib as continuation/maintenance is expected to be longer than with midostaurin, thus necessitating additional monitoring. This difference in duration of treatment may impact healthcare resource utilisation.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology will be exclusively used in specialist Haematology units within secondary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional facilities or training are required, with the exception of a greater need for ECG and blood count monitoring in the continuation/maintenance phase of therapy.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In the absence of a direct comparison with the current standard-of-care, it is challenging to determine whether the benefit with the addition of quizartinib to chemotherapy in AML with *FLT3*-ITD will surpass that observed with midostaurin and intensive induction and consolidation chemotherapy, or as post-chemotherapy maintenance compared to midostaurin or oral azacitidine, and in the post-transplant setting, relative to sorafenib.
11a. Do you expect the technology to increase length of life more than current care?	I anticipate that survival will be similar to that observed with current care for the entire cohort of patients with AML and *FLT3*-ITD to whom this new technology (drug treatment) is applicable. However, in the absence of a direct comparison with current care and detailed molecular analysis, it is challenging to determine whether sub-groups of patients, such as those with a particular subtype of *FLT3*-ITD (e.g., based on insertion site), will derive greater clinical benefit from quizartinib compared to midostaurin.
11b. Do you expect the technology to increase	While data on the quality of life with quizartinib are not currently published, it is unlikely that significant improvements in health-related quality of life over midostaurin-containing treatment, considered current care, will be observed for two reasons: 1. Demonstrating objective, statistically significant improvements in QoL with

health-related quality of life more than current care?	newer therapies in AML has been challenging, even with agents improving survival and reducing the burden of care, which is often perceived to enhance QoL. 2. To my knowledge, there is no direct comparison of QoL in recipients of quizartinib or midostaurin combined with chemotherapy.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In the absence of a direct comparison with current care, it remains unclear whether there are specific patient sub-groups that would benefit more from quizartinib-containing treatment. There is a suggestion that the new technology (quizartinib) may offer greater benefits to patients with *FLT3*-ITD AML compared to current treatment with midostaurin. Unlike the QuANTUM-First trial, which exclusively recruited patients with FLT3-ITD, RATIFY included patients with both *FLT3*-ITD and TKD mutations. It has been proposed that the survival benefit with midostaurin in RATIFY might be confounded by a relatively greater reduction in the risk of death in FLT3-TKD patients (35%) compared to those with *FLT3*-ITD (20%). However, this post hoc, numerically imbalanced sub-group analysis, which does not reach statistical significance, requires cautious interpretation. QuANTUM-First included patients over 60 years of age, in contrast to RATIFY, which had an age restriction (under 60 years) for recruitment. While patients up to 75 years were enrolled in QuANTUM-First, the difference in outcomes between quizartinib or placebo did not reach statistical significance in the subgroup of older patients. This raises debate about whether the survival benefit for the entire cohort of patients can be extrapolated to suggest similar benefits for older patients. Additionally, there is a further caveat to consider: approval for the use of midostaurin following chemotherapy is currently age-agnostic, and is supported by the results of a Phase 2 study in older patients (albeit compared against a historical cohort of patients), as well as by a recent single arm, phase 3b study that demonstrates relative safety, even with an extended course of midostaurin.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed,	There are no significant new tests required beyond current care, but in the continuation/maintenance phase of treatment, which can extend post-allogeneic stem cell transplantation (alloSCT) for up to 36 cycles, additional ECGs will be necessary. Rates of anaemia and rash may be lower with quizartinib compared to midostaurin.

additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Guidance to start or stop therapy with the new technology will generally mirror current therapy, except for the initiation or re-initiation of continuation therapy after an allogeneic stem cell transplant with quizartinib. Typically, therapy is discontinued due to reasons of disease progression or adverse events
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Due to the extended continuation/maintenance phase of treatment with quizartinib, a greater number of hospital visits and the need for monitoring (e.g., ECG) will be required compared to current care, potentially influencing QALY. However, it is noteworthy that in the pivotal studies, less than 50% of patients who initiated induction therapy proceeded to post-consolidation continuation/maintenance therapy, with subsequent drug discontinuation rates approaching 43% and 54% in the quizartinib arm of QuANTUM-First and the midostaurin arm of RATIFY, respectively. Additionally, the toxicity profile of quizartinib maintenance is likely to be superior to oral azacitidine and sorafenib.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Given the absence of a direct comparison between the new technology (drug) and current care, it is challenging to determine whether the new technology represents an improvement on existing care. The addition of quizartinib to chemotherapy does, however, provide an alternative option for patients with AML characterized by *FLT3*-ITD who may be intolerant to current care with midostaurin (until transplantation) or maintenance/continuation therapy with azacitidine (in non-transplant candidates) or sorafenib (in the post-transplant setting).
16a. Is the technology a 'step-change' in the management of the condition?	While quizartinib offers an alternative option to patients who may be intolerant of current care, for the reasons described previously, it cannot be considered a 'step-change' in the management of AML with *FLT3*-ITD.

16b. Does the use of the technology address any particular unmet need of the patient population?	Quizartinib presents a viable option for individuals intolerant of current care. Further data on its utility in disease control in specific patient subsets, or its impact on quality of life, would be essential for considering it as a potential new standard treatment
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The frequency of rash and severity of anaemia with quizartinib may be lower than with midostaurin-containing therapy, the current treatment. While neutrophil and platelet recovery might take slightly longer compared to placebo (based on QuANTUM-First and RATIFY), the impact on the duration of hospitalization and quality of life remains unclear. It is worth noting that there will be a greater requirement for monitoring with quizartinib, given the longer prescribed duration of therapy as continuation/maintenance compared to midostaurin

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The comparator arm in the clinical trial is not considered standard care in the UK, as DA + midostaurin is now the standard treatment (see response to question 9). There are differences in the induction chemotherapy backbone of the trial, which used daunorubicin or idarubicin for 3 days with cytarabine as a continuous infusion schedule at 100 or 200mg/m^2/day for 7 days. This contrasts with the regimen used in the UK, which employs 3 days of daunorubicin and 10 days of cytarabine at 200mg/m^2/day in divided doses (DA 3+10), followed by a second anthracycline-containing induction regimen, even in patients achieving complete remission. In contrast, in the trial, a second anthracycline-containing cycle was administered only to patients with resistance disease after the first cycle of induction. However, incorporating the new drug into the UK schedule of chemotherapy following induction or consolidation is not expected to result in a loss of efficacy or increased toxicity, similar to RATIFY. While there were slight differences in the number of consolidation cycles permitted in the trial compared to UK practice, some aspects of the QuANTUM-First trial align more closely with contemporary UK practice than RATIFY. For instance, a higher percentage of patients received consolidation with allogeneic stem cell transplantation (~40%) in the first complete remission, in line with current UK practice, compared to RATIFY (~25%).
18a. If not, how could the results be extrapolated to the UK setting?	While the treatment can be incorporated relatively easily into UK practice, similar to midostaurin, prospectively identifying the patient subset that could benefit more from quizartinib than midostaurin will be challenging

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, cumulative incidence of relapse and quality-of-life are important outcomes and have been measured. However, quality-of-life data, to my knowledge are yet to be published.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As of now, there are insufficient data on the use of quizartinib in this setting to offer a comment. However, results from a Phase 3b study involving current care midostaurin) have been published recently. Unlike the original licensing study (RATIFY), this study includes older patients, and no new safety or efficacy signals of concern have been identified, even if tolerance of therapy due to side effects was poorer in patients over 60 years of age
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The role of maintenance treatment in these patients, especially those proceeding to allogeneic stem cell transplantation and as post-transplant maintenance, remains unclear. Potential confounders include the co-mutation profile, particularly the co-existence of NPM-1 mutations, the contribution of *FLT3*-ITD to the disease burden (with the 'hard-to-quantify' variant allele frequency as a surrogate), relapse without detectable *FLT3*-ITD, and disease sensitivity to therapy using 'measurable residual disease' (MRD) as a marker of the depth of response. Accurate MRD measurements in *FLT3* mutant AML are challenging but may be of prognostic relevance. In the future, MRD could serve as a predictive biomarker to deliver risk-adapted maintenance therapy.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA722?	I am unable to draw a direct link between NICE technology appraisal guidance TA722 and this submission. However, recent Phase 3b trial data with the comparator, midostaurin, have been published (see response to 18d). Additionally, new comparators may include the use of gilteritinib maintenance after allogeneic stem cell transplantation (data presented recently and anticipated to be published over the next few months), and up-front and maintenance treatment with gilteritinib, based on the ongoing randomized phase 3 clinical trial comparison with midostaurin. Soon to be published data from the UK NCRN AML19 trial on the use of FLAG-Ida as intensified chemotherapy (without a *FLT3* inhibitor), and DA combined with midostaurin and gemtuzumab will be relevant new comparators.

21. How do data on real-world experience compare with the trial data?	There are few 'real world' data on the use of quizartinib with intensive chemotherapy in previously untreated patients with AML and *FLT3*-ITD. Outcomes in the placebo arm of the trial appear to be consistent with findings from studies.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are some data involving sub-groups, which should be interpreted with caution. In RATIFY (which forms the basis for current care), the placebo group contained more women (~60%) (p=0.04) than in the midostaurin arm, and midostaurin appeared to associate with a survival improvement in males but not females. In contrast, quizartinib may favour survival in (self-identified) females, but there are insufficient data to make treatment recommendations based on sex, world regions, or ethnicity.
22b. Consider whether these issues are different from issues with current care and why.	The amount and quality of data are insufficient for this to be a consideration at present.

Topic-specific questions

23. What proportion of people with AML have maintenance therapy and how is this decision made?	Maintenance' therapy has gained approval in the UK, primarily based on the survival benefit observed with CC-486 in the QUAZAR study. Notably, the study design did not test CC-486 as maintenance after standard post-remission therapy or as an alternative to standard post-remission therapy, with only 78% of patients in complete remission. In my view, the use of CC-486 is more appropriately termed 'continuation' therapy for AML in patients unable to complete post-remission therapy, rather than 'maintenance' therapy. This distinction is crucial when commenting on the proportion of AML patients who may proceed to 'maintenance therapy' after intensive post-remission chemotherapy, including alloSCT. Consequently, I have excluded CC-486 from this comparison. Based on clinical trial data and my experience with individuals discontinuing intensive therapy following induction for various reasons, I anticipate at least 70% of patients to receive post-remission, intensive consolidation. In trials on continuation/maintenance therapy with midostaurin or quizartinib, approximately 30-40% of those starting intensive induction therapy received maintenance therapy. I would consider multiple factors in a decision for maintenance therapy (as per the definition above) in AML, including disease control, MRD status (if an appropriate marker has been identified), alloSCT, its complications, and the risk profile of the drug used in maintenance therapy.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Quizartinib with intensive chemotherapy and alloSCT prolongs survival and reduces relapse in AML with *FLT3*-ITD. • • Current standard is midostaurin with chemotherapy, showing similar survival benefit (as quizartinib) in placebo-based trials. • • Unclear if quizartinib surpasses midostaurin benefits without head-to-head comparison. • • Censoring at transplantation suggests a potential numerical but not statistically significant survival benefit for both inhibitors. • • The role of maintenance therapy with both inhibitors and impact on QoL remain unclear.

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Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Clinical expert statement

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The deadline for your response is **5pm** on **Friday 26 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating newly diagnosed FLT3-ITD positive acute myeloid leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Priyanka Mehta
2. Name of organisation	University Hospitals Bristol and Weston NHS Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acute myeloid leukaemia? ☒ A specialist in the clinical evidence base for acute myeloid leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA

8. What is the main aim of treatment for newly diagnosed FLT3-ITD positive acute myeloid leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cure in the younger and fit patients; prolonging survival in the elderly and frail patients
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Complete remission, undetectable disease with a significant reduction in the risk of relapse
10. In your view, is there an unmet need for patients and healthcare professionals in newly diagnosed FLT3-ITD-positive acute myeloid leukaemia?	Yes, there is a significantly high risk of relapse and thereby, the need for salvage treatments and mortality
11. How is newly diagnosed FLT3-ITD-positive acute myeloid leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients fit for intensive chemotherapy, get combination of Daunorubicin and cytarabine (DA) with Midostaurin (oral FLT3 inhibitor) through induction and consolidation courses. For patients who do not get a transplant, they are eligible for Midostaurin maintenance for a year. For patients who get a transplant, Midostaurin is not approved for maintenance but recently, Sorafenib, another Flt 3 inhibitor, has been made available in this situation. For patients unfit for intensive chemotherapy, who receive less intensive treatments like Venetoclax+ Azacytidine/ low dose cytarabine, there is no targeted flt3 inhibitor approved for use in combination in the frontline setting. The pathway of care is clear and there is consensus on treatment mentioned above, although there remains ambiguity/ subjectivity in deciding if a patient is fit or unfit for intensive treatment I do not think there is any significant variation or difference of opinion across the NHS and since the approval of Midostaurin, DA+Mido has been the std of care for fit patients. Use of Sorafenib post transplant has been less uniform as it was previously only available on a compassionate access programme and its use was limited by the toxicity observed in the post transplant settings.

	Impact of technology on the current pathway of care: Use of Quizartinib in combination with DA would mean a more potent, second generation Flt3 ITD inhibitor could be administered throughout the induction, consolidation and maintenance treatment in non transplant and transplant patients. However, this would be for the Flt3 ITD mutated patients which is ~70% of the Flt3 mutated patients. The Flt3 TKD mutated patients would follow the current pathway of DA+midostaurin outlined above. This is not a concern as Flt3 TKD mutation does not carry the same adverse prognostic features as Flt3 ITD mutation There would be consistency and hence safety (in prescribing, administering, monitoring) with the same drug throughout the course of treatment as opposed to current pathway for transplanted pts, who currently switch from Midostaurin to Sorafenib post transplant. Quizartinib studies have data on patients upto the age of 75 whilst Midostaurin licensing study had data only upto the age of 60. This is important in AML where the median age of presentation is 68 yrs. Although no direct comparison is available and accepting the caveats of comparing different trials, the overall survival and relapse free survival with Quizartinib appears superior to Midostaurin for Flt3 ITD mutated pts. Any reduction in relapse for these patients would mean reduction in the need for salvage chemotherapy and mortality. The tolerability of the two drugs is similar in trials and in my clinical experience of using these drugs. However, sorafenib post transplant is relatively poorly tolerated.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Currently the non transplant patients are receiving oral Midostaurin, initially as inpatient alongside intensive chemotherapy and then in consolidation and maintenance as outpatients, which requires outpatient administration and monitoring of blood tests and ECG's Post transplant patients receive Sorafenib which requires similar monitoring Quizartinib is also oral preparation and will require similar initial inpatient alongside intensive chemo and subsequent outpatient administration and monitoring Quizartinib will be delivered in haematology and/or transplant wards and clinics, similar to Midostaurin and Sorafenib No additional investment in facilities, equipment or training will be required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The current std of care using Midostaurin, still results in high relapse rates and the trial had shown 40% relapse by end of 2 years (and likely to have been higher if restricted to Flt3 ITD population which has poorer prognosis). The median disease free survival with Midostaurin was 25.9 months as compared to 15.5 with placebo, in the population that included Flt3 ITD and Flt3 TKD mutated pts Quizartinib has been shown to increase relapse free survival by 3 times as compared to placebo and this benefit is maintained over 24 month period. Also, this is entirely in the ITD mutated pts who carry poorer prognosis as compared to the TKD mutated pts As the main cause of death in this population is relapse, a 3x increase in relapse free survival would mean an increased length of life more than current care. Reduction in relapse would directly improve health related QoL as it would mean lesser chance of requiring further salvage chemotherapy/ transplant/ DLI's etc

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The subgroup of patients with Flt3 TKD mutations would not be eligible for this treatment The older population of pts >60 would benefit from this treatment as shown in the Quizartinib trial. These patients were not included in the Midostaurin trial
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Use of Quizartinib should not be any different to use of current std Midostaurin for healthcare professionals No additional tests or training or pharmacovigilance will be required beyond current practice
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting and stopping rules will be as per QUANTUM FIRST trial methods Screening for safety/ side effects and relapse would be similar to current std of care with Midostaurin or Sorafenib post transplant
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Reducing the risk of relapse is a significant improvement for patients, psychologically and a substantial health related benefit. There are no other additional factors affecting QALY
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This technology is a step change as it uses a significantly more potent, second generation Flt3 inhibitor, across a much larger age range and uniformly through all stages of treatment ie induction, consolidation and maintenance in transplanted and non transplanted patients

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The largest unmet need in this population of patients is death due to disease relapse. Quizartinib has been shown to significantly reduce the risk of relapse in the FLT3-ITD mutated AML patients, more than the current std of care This trial also brings a step change in the monitoring of MRD in this group of AML pts using Next Generation Sequencing of Flt3 ITD
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Quizartinib will require blood tests and ECG monitoring for side effects, similar to Midostaurin. Longer term follow up of patients in trials has not shown any new safety signals/ toxicity. There should be no adverse effects on patient's quality of life compared to current std
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials reflect current standard in relation to use of the backbone of Daunorubicin and Cytarabine. It also represents the UK population more closely with regards to the age range included in the trial ie 18-75 yrs. However, the trial SOC arm had DA+ placebo and the current SOC in the UK is DA+Midostaurin Extrapolating results to the UK population would require comparison of the QUANTUM-First and the Ratify trials, as best as possible The most important outcomes of the OUANTUM first trial and it's post hoc analysis includes: Improved Overall Survival Improved Relapse Free Survival Acceptable safety and tolerability Surrogate outcome measure of measuring FLT3 ITD using NGS was reported recently at EHA 2024:Post hoc analysis revealed longer OS in patients treated with quizartinib versus placebo, irrespective of MRD status pre-allo-HSCT; although the survival benefit was more pronounced in those who were MRD+ pre-allo-HSCT Post hoc analysis also reported on safety data which showed no new safety signals/ adverse effects since the first report in trial

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA523]?	The UK NCRI AML 18 trial reported on use of Quizartinib in AML pts >60 years, alongside multiple other agents, at EHA 2023
23. How do data on real-world experience compare with the trial data?	Not aware of real world data
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	No specific equality issues identified. Trial data includes older pts upto the age of 75 which is an improvement

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

QUANTUM First trial includes a wider age range including older patients upto 75 yr old, which is representative of the AML population

Quizartinib, as a second generation more potent Flt3-ITD inhibitor, combined with DA significantly prolongs overall survival as compared to placebo

Quizartinib with DA significantly reduces the risk of relapse as compared to placebo in the trial, as well as compared to Midostaurin in the RATIFY trial

Clinically meaningful improvements in relapse-free survival, reduced cumulative incidence of relapse, increased duration of complete remission, and reduction in MRD underpin the overall survival benefit with Quizartinib.

Quizartinib has a generally manageable safety profile, with no new safety signals identified

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Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Clinical expert statement

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Part 1: Treating newly diagnosed FLT3-ITD positive acute myeloid leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Steven Knapper
2. Name of organisation	Cardiff University / Cardiff & Vale University Health Board
3. Job title or position	Professor in Haematology / Honorary Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acute myeloid leukaemia? ☒ A specialist in the clinical evidence base for acute myeloid leukaemia or technology? ☒ Other (please specify): Current Deputy Chair of UK AML Research Network (formerly NCRI AML Working Group)
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil to disclose

8. What is the main aim of treatment for newly diagnosed FLT3-ITD positive acute myeloid leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The principal aim for the majority of patients with FLT3-ITD positive AML is to cure the disease. This aim currently applies chiefly to those patients who are considered fit enough to take an intensive treatment approach with cycles of intensive chemotherapy followed, in selected cases, by allogeneic stem cell transplant. To achieve this aim, in these patients, first requires establishment of disease remission; this is followed by consolidation therapy aimed at reducing the chances of relapse (consolidation includes one or more of: further cycles of intensive therapy, maintenance therapy with tyrosine kinase inhibitors, allogeneic stem cell transplant). For older, frailer patients not considered suitable for an intensive treatment strategy, treatment is primarily aimed at achieving disease stability while maintaining quality of life. This group is outside scope of current appraisal.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant response would be achievement of complete remission. Even more significant is achievement of MRD (measurable residual disease) negative remission. MRD quantified in FLT3+ patients primarily using NPM1 qPCR (in the approx. 50% with co-mutations of NPM1) or by flow cytometric techniques in the others. FLT3 NGS MRD is currently under development. Duration of response then becomes the most clinically significant marker (overall survival, prevention of relapse).
10. In your view, is there an unmet need for patients and healthcare professionals in newly diagnosed FLT3-ITD-positive acute myeloid leukaemia?	Yes. Longer term survival rates remain only approximately 50% in this subgroup of patients, so there are clearly improvements still to be achieved. We are seeing incremental improvements in overall survival of FLT3+ AML patients in successive clinical trials over time.
11. How is newly diagnosed FLT3-ITD-positive acute myeloid leukaemia currently treated in the NHS?	The main guidelines that are in place are European Leukaemia Net Guidelines – these are generally adhered to in the UK for 'standard of care' outside clinical trials. There are no active BCSH guidelines in this group.

• Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently, standard of care for FLT3-ITD patients who are considered suitable for intensive chemotherapy (IC) is DA (Daunorubicin plus Cytarabine), with the NICE-approved tyrosine kinase inhibitor Midostaurin. Standard of care for patients receiving 'chemotherapy only' is 4 cycles of IC (2 x DA followed by 2 x high dose cytarabine) each of which is followed by 14 days of midostaurin. Patients then receive 12 months of maintenance midostaurin. Many patients in the FLT3-ITD group go on to receive allogeneic stem cell transplant in 1st complete remission. This generally applies to those with FLT3+, NPM1 negative disease; also those with NPM1 co-mutated disease who fail to achieve blood NPM1 qPCR negativity following cycle 2 of IC. Allogeneic SCT is generally performed following 2 or 3 cycles of IC and replaces the need to give later cycles of IC. Midostaurin is not currently approved as maintenance therapy post-transplant. Many centres access other tyrosine kinase inhibitors (such as sorafenib) to use as post-transplant maintenance. This pathway of care is fairly well defined. However, the recent NCRI AML19 trial suggested that FLAG-Ida may be a better IC backbone (than DA) for FLT3+ patients ***(Russell. J Clin Onc. Apr 2024; 42(10): 1158-1168).*** Also, longer term outcomes in FLT3+ AML were substanailly better in AML19 with both DA+Mylotarg and FLAG-Ida-Mylotarg (no TKI), than historically seen with DA-Midostaurin in the RATIFY trial. A 3-way prospective comparison of DA-Mido, DA-Mido+Mylotarg and FLAG-Ida-Mylotarg-Mido is shortly to begin at 80+ sites in UK, Denmark and New Zealand – this is the Optimise-FLT3 study (n=390, to recruit from Q4 of 2024). Were Quizartinib to be approved following the current appraisal, it would give the option of using DA-Quiz instead of DA-Midostaurin in frontline treatment. Unlike midostaurin, this would be limited to patients with FLT3-ITD mutations (not those with FLT3-TKD mutations). I am really quite uncertain of the impact of this on the

	pathways of care, as many UK patients will be going into the Optimise-FLT3 study over the next 3-4 years, and there has not yet been any prospective comparison of DA-Mido with DA-Quiz – so nobody yet knows whether so called '2nd generation' TKIs hold any advantage over '1st generation' drugs such as midostaurin. So the uptake of quizartinib among the AML-treating community is rather uncertain.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Resource use would probably not be much difference with quizartinib compared with midostaurin. I wouldn't anticipate much change in rates of patients requiring allogeneic stem cell transplant in 1st remission. The main cost differences are likely to lie in exactly how quizartinib is approved for use as maintenance therapy, given that – were this to be approved for 2yrs (or longer) then the overwhelming majority of drug would be used in the maintenance setting, so that is where the main costs will lie. I'm not aware of any convincing clinical evidence (yet) of a clear benefit from using quizartinib maintenance (either with or without accompanying allogeneic transplant). In the Quantum-first study, patients actually received relatively little maintenance exposure (median study drug exposure was only 10.7 weeks) – and that would have included 2 weeks after each cycle of intensive chemotherapy; so it is not possible to draw too many inferences about the effectiveness of maintenance quizartinib in that setting. Ideally a separate placebo controlled randomisation to maintenance vs placebo/not would have been included.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	There is insufficient evidence to say. There has not yet been any prospective comparison of IC+quizartinib with current standard of care (IC+midostaurin). A prospective study (run by HOVON group) has just competed recruitment comparing DA-Midostaurin with another 2nd generation FLT3 TKI Gilteritinib (ie.

• Do you expect the technology to increase health-related quality of life more than current care?	DA-Gilteritinib), and the results of that study will potentially give the first prospective data comparing 1st vs 2nd generation TKIs used alongside IC. The Quantum-first study did (unlike RATIFY study) include patients over the age of 60 where it appeared to show benefit over placebo, although numbers in the >60yrs age group were insufficient to demonstrate statistically significant benefit in older patients. It is, however, reasonable to postulate (as was the case in the midostaurin NICE appraisal) that benefits can be applied to both <60 and >60 patients. I'm not aware of evidence demonstrating QoL advantage over current care. Both quizartinib and midostaurin are reasonably well tolerated. Certainly there is some cardiac / QT signal with quizartinib that requires additional ECG monitoring, over and above that with midostaurin so that would potentially require more regular follow-up and hospital attendance than is currently the case with midostaurin – this might negatively impact return to work/normal activities.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Quizartinib is restricted (by its mechanism of action) to those AML patients who have FLT3 mutations of ITD subtype – about 20-25% of the total. Midostaurin is currently approved for FLT3 mutated patients of both types – also TKD mutations (accounting for a further 7-10% of patients) – roughly one-third in total.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Probably not much different – but slightly more difficult. There is likely to be some need for additional ECG monitoring. The current product literature recommends that ECGs are performed prior to starting quizartinib and then on a weekly basis while on quizartinib during induction and consolidation cycles of IC.

acceptability or ease of use or additional tests or monitoring needed)	During maintenance ECGs are recommended weekly for the first month and also more frequently if patients are on any concomitant QT prolonging medications.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients would have their ongoing remission status monitored in the usual way – via a combination of blood tests and bone marrow surveillance (surveillance marrows mainly for those with NPM1 co-mutation at diagnosis). If maintenance quizartinib were to be used, this would generally only be stopped if not tolerated, or tests confirmed relapsing disease.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Without any prospective / direct clinical trial comparison to current standard of care it is really not possible for me to conclude that this new technology represents a 'step change' in management of AML as we simply don't know whether it is better to combine 1st or 2nd generation TKIs with intensive chemotherapy. The results of RATIFY and QUANTUM-First are broadly similar. If quizartinib were to be approved for IC-fit patients >60yrs, then it would represent a potential advance for those patients (although they currently able to access midostaurin as NICE approval of midostaurin is 'age agnostic').

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	It is generally well tolerated. Main concerns are the QT prolongation side effects which are subject to additional safety monitoring (see above)
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials broadly reflect UK clinical practice. There are some differences with how backbone 'DA' chemotherapy is generally used in the UK in comparison to the standard '7+3' used in QUANTUM-First. UK patients generally receive higher doses of cytarabine in induction (as DA '3+10') and generally receive 2 cycles of DA induction, rather than the single cycle generally favoured in international studies. I'm not aware of adverse effects that have come to light subsequent to the published studies.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA523]?	No
23. How do data on real-world experience compare with the trial data?	I'm not aware of real-world data published in the setting of Quizartinib therapy / FLT3-ITD AML
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into	There were some sub-group data in both RATIFY and QUANTUM-First to suggest differential benefits according to male/female. I don't feel that the AML

account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	treating community is convinced by these sub-group differences enough to favour one drug approach over the other so it is unlikely to be clinically relevant going forward. I'm not aware of any other equality / diversity issues arising.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Broadly speaking the efficacy data with IC+Quizartinib in QUANTUM-First are similar to those published with IC+Midostaurin in RATIFY

There hasn't yet been a completed prospective evaluation of Midostaurin vs '2nd generation FLT3 inhibitor' in FLT3-mutated AML, so any advantages of '2nd generation' drugs in frontline combination treatment remain speculative

Although there is a need for effective maintenance therapy (post-chemo and post-transplant) in FLT3-mutated AML, the evidence is currently lacking and only limited conclusions can be drawn from QUANTUM-First in this regard

Some additional QT issues with Quizartinib that require additional monitoring and infrastructural requirement for this to be done safely, especially in the setting of maintenance therapt

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Single Technology Appraisal

1. Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with FLT3-ITD-positive acute myeloid leukaemia or caring for a patient with FLT3-ITD-positive acute myeloid leukaemia. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 26 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Part 1: Living with this condition or caring for a patient with FLT3-ITD-positive acute myeloid leukaemia

Table 1 About you, FLT3-ITD positive acute myeloid leukaemia, current treatments and equality

1. Your name	Esther Beswick
2. Are you (please tick all that apply)	☐ A patient with FLT3-ITD-positive acute myeloid leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with FLT3-ITD-positive acute myeloid leukaemia? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): A patient with a diagnosis of AML which was not FLT3-ITD positive
3. Name of your nominating organisation	Leukaemia Care
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing this statement
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). In addition to my personal experience of AML, I am also a

	qualified nurse currently working on a clinical haematology ward, providing care to patients with AML and a range of other blood cancers. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with FLT3-ITD-positive acute myeloid leukaemia? **If you are a carer (for someone with FLT3-ITD-positive acute myeloid leukaemia) please share your experience of caring for them**	Living with AML was an entirely traumatic experience for myself and my family both physically and mentally. I was diagnosed and admitted as an emergency presentation during the initial stages of Covid in 2020 which brought its own additional challenges. Although the chemotherapy treatment I received was physically gruelling and had unpleasant and unwanted side effects, the emotional aspects of the disease were equally if not more distressing and took longer to recover from than the physical aspects. Due to having low risk mutations after genetic analysis, I received the traditional 7+3 chemotherapy – 7 days of cytarabine and 3 days of Danorubicin plus an additional targeted therapy drug called Mylotarg. These medications were all administered intravenously over a prolonged period of time (eg 1st cycle of cytarabine 24 hours per day for 7 days), which meant that I had to stay in hospital for an extended time. Each treatment resulted in an infection requiring additional hospital stays, and I also spent several days per week on the hospital day unit having supportive treatment in the form of blood and platelet transfusions. Thankfully my treatment was successful and I have been in remission for almost 4 years now and I was very fortunate that I did not need to go ot to have a stem cell transplant. I have returned to full health and strength and have not been left with any unwanted side effects for which I am very grateful. As a result I was able to return to my job as a nurse, and am now working on the same haematology ward where I received my chemotherapy treatment and am able

	to care for patients who are going through the same or similar treatments as myself for AML and other blood cancers.
7a. What do you think of the current treatments and care available for FLT3-ITD-positive acute myeloid leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) Although there are some other treatments available for FLT3-ITD positive leukaemias, these are limited and may be less effective than standard treatments, which may result in relapse, or not be effective in achieving remission in the first place. b) Having been through treatment for AML, and having experienced the inevitable side effects that comes with this, I have a unique insight into the treatment available for AML. Speaking personally, the more treatment options available, the better, particularly if these treatments come with reduced side effects and/or increased rate of survival as this allows patients to have some control over the choice of their treatment.
8. If there are disadvantages for patients of current NHS treatments for FLT3-ITD-positive acute myeloid leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Some current treatments may require longer inpatient hospital admissions which can have a negative impact on a patients quality of life as it takes them away from their family and friends for longer periods. This can also negatively impact mental health during what is an already difficult and traumatic experience. Current treatments also may have a higher relapse rate or increased risk of unwanted side effects compared to newer treatments such as these being appraised.
9a. If there are advantages of quizartinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does quizartinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Advantages of Quizartinib include the fact that it can be used before a stem cell transplant, whereas its comparators oral azacitidine and midostaurin cannot. This is a definite benefit for patients with high risk of relapse where a stem cell transplant may become necessary. Quizartinib is also an oral therapy which means it can be taken at home which reduces the need for long inpatient stays. Both of these advantages are of benefit to patients and speaking from personal experience, I would definitely have preferred an oral treatment which could be taken at home in comparison with an intravenous therapy which would have to be administered in hospital, likely requiring an extended inpatient admission.

10. If there are disadvantages of quizartinib over current treatments on the NHS please describe these. For example, are there any risks with quizartinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	All drugs have some disadvantages and side effects, in the case of Quizartinib, research into its effectiveness in FLT3 mutation is still ongoing. Quizartinib can also cause a prolonged QT interval on ECG which can have subsequent adverse effects, however most patients would be willing to accept the risk of some side effects to have more choice of treatment available – particularly in a group of patients who are at high risk of relapse.
11. Are there any groups of patients who might benefit more from quizartinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with a FLT3 mutation have a worse prognosis than some other mutations in AML so any additional treatment options would be welcomed. As previously mentioned, the fact that this is an oral therapy rather than intravenous would be likely to be a significant benefit to patients also, particularly if this reduces or even eliminates the need for additional inpatient admissions.
12. Are there any potential equality issues that should be taken into account when considering FLT3-ITD-positive acute myeloid leukaemia and quizartinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	All patients should have the right to make an informed choice about their treatment – and should be offered information about all the options available for their specific condition. Patients have a right to choose what is the right treatment path for them – taking into account the possibility of side effects/rate of relapse and overall survival. For some patients, the choice of best supportive care may be the right choice for them, regardless of age. Treatment for AML is gruelling for anyone – even those who were young and fit (as I was) – so it is understandable that some patients may choose not to go ahead with such treatments.

13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- AML is a physically and emotionally traumatic illness, not just for patients but also for their families due to the prolonged nature of its treatment and its associated side effects
- AML is a complex disease which requires intensive treatment – some treatments cannot be tolerated by certain patients so more options for treatment need to be made available to increase chance of survival.
- Quizartinib is a targeted treatment for patients with the FLT3 mutation which has a much poorer prognosis than other mutations.
- Quizartinib can be given to patients prior to having a stem cell transplant if required, whereas the current treatment for FLT3 mutation cannot.
- All AML patients should be able to make informed decisions about their treatment and should be offered all available treatments specific to their disease/mutation for consideration.

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

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None

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Rider on responsibility for report

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.

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Contributions of authors

Sarah Nevitt oversaw the review of the clinical effectiveness evidence, performed the critical review of the indirect treatment comparisons, conducted EAG additional analyses, contributed to drafting Section 3 of the report, commented on drafts of the report and takes joint responsibility for the report as a whole.

Alexis Llewellyn performed the critical review of the clinical effectiveness evidence, drafted Section 2 and contributed to drafting Section 3 of the report

Nyanar Jasmine Deng performed the critical review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 4, 5, 6 and 7 of the report

Diarmuid Coughlan performed the critical review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 4, 5 and 6 of the report

Sumayya Anwer performed the critical review of the clinical effectiveness evidence and contributed to drafting Section 3 of the report

David Marshall performed the critical review of the clinical effectiveness evidence and contributed to drafting Section 3 of the report

Melissa Harden reviewed the systematic review searches, wrote sections of the report pertaining to the searches and provided editorial support

Robert Hodgson oversaw the review of the cost effectiveness evidence, conducted EAG additional analyses, contributed to drafting Sections 4, 5, 6 and 7 of the report, commented on drafts of the report and takes joint responsibility for the report as a whole.

Note on the text

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

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANC	Absolute neutrophil count
HSCT	Hematopoietic stem cell transplantation (allogeneic)
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukaemia
AR	Allelic ratio
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
BSC	Best supportive care
CDSR	Cochrane Database of Systematic Reviews
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CfB	Change from baseline
CI	Confidence interval
CIR	Cumulative incidence of relapse
CNS	Central nervous system
CR	Complete remission
CRc	Composite complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete neutrophil or platelet recovery
CR1	First CR
CR2	Second CR
CS	Company's submission
CSR	Clinical study report
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DFS	Disease-free survival
DS	Daiichi Sankyo
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ELN	European LeukemiaNet
ELPD	Expected log predictive density
EMA	European Medicines Agency
EMD	Extramedullary disease
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer core quality of life questionnaire
EQ-5D-3L	EuroQoL-5D-3L
EQ-5D-5L	EuroQoL-5D-5L
ERG	Evidence review group
ESMO	European Society for Medical Oncology
ESS	Estimated sample size
FDA	United States Food and Drug Administration
FLAG-Ida	Fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor
FLT3	FMS-like tyrosine kinase 3 (refers to the protein)
FLT3	FMS-like tyrosine kinase 3 (refers to the gene)
FLT3+	FMS-like tyrosine kinase 3 positive
FLT3i	FMS-like tyrosine kinase 3 inhibitor
FLT3-ITD	FMS-like tyrosine kinase 3 internal tandem duplication
FLT3-ITD+	FMS-like tyrosine kinase 3 internal tandem duplication positive

Abbreviation	Definition
FLT3-TKD	FMS-like tyrosine kinase 3 tyrosine kinase domain
FMS	Feline McDonough sarcoma
GBP	Great British Pound
GVHD	Graft-vs.-host disease
HCRU	Healthcare resource utilisation
HEOR	Health economics and outcomes research
HiDAC	High-dose cytarabine
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplantation
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ICUR	Incremental cost-utility ratio
IDAC	Intermediate-dose cytarabine
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
IPSW	Inverse propensity score weighting
IQR	Interquartile range
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITD	Internal tandem duplication
ITF	Induction treatment failure
ITT	Intent-to-treat
KM	Kaplan-Meier
LDAC	Low-dose cytarabine
LR	Log-rank
LVEF	Left ventricular ejection fraction
MAIC	Matching adjusted treatment indirect comparison
MCID	Minimal clinically important difference
MDS	Myelodysplastic syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MIDO	Midostaurin
MLFS	Morphologic leukaemia-free state
ML-NMR	Multilevel network meta-regression
MMRM	Mixed-effects model for repeated measures
MPN	Myeloproliferative neoplasm
MRD	Minimal or measurable residual disease
MUGA	Multi-gated acquisition scan
NA	Not applicable
ND	Newly diagnosed
NE	Not estimable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMR	Net monetary benefit
NPM1	Nucleophosmin 1
NR	Not reported
NYHA	New York Heart Classification
ONS	Office for National Statistics
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PBO	Placebo
PH	Proportional hazards
PRO	Patient-reported outcome

Abbreviation	Definition
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned Survival Model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
QT	Interval between the start of the Q wave and the end of the T wave
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
QUIZ	Quizartinib
RCT	Randomised controlled trial
RDI	Relative dose intensity
RFS	Relapse-free survival
RMST	Restricted mean survival time
RNA	Ribonucleic acid
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
R/R	Relapsed/refractory
RTK	Receptor tyrosine kinase
Relapse1	First relapse
Relapse2	Second relapse
SAE	Serious adverse event
SC	Standard chemotherapy
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
TKD	Tyrosine kinase domain (refers to the protein)
TKD	Tyrosine kinase domain (refers to the gene)
TP	Transition probability
TSD	Technical support document
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAF	Variant allele frequency
VAS	Visual analogue scale
VAT	Value added tax
WBC	White blood cell
WHO	World Health Organization
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

Overview of the EAG's key issues

Summary of key issues

Issue ID	Summary of issue	Report sections
1	**No robust evidence of improved efficacy of quizartinib compared to midostaurin across all treatment phases**	3.4.1, 3.5.1
2	**Limited comparability of QuANTUM-First and RATIFY**	3.4.1
3	**Company MAICs do not reflect the correct target population for decision making**	3.4.1
4	**Incorrect application of population-adjusted ITC results in the economic model**	3.5.1
5	**No robust evidence of improved efficacy and safety of quizartinib in the post-HSCT maintenance setting**	2.3, 3.2, 3.2.4
6	**Validity of model predictions**	4.2.2
7	**Appropriateness of using a state transition model to evaluate second-line treatment/modelling of induction health state**	4.2.2, 4.2.6
8	**Inconsistency between modelled outcomes and outcomes evaluated in ITC**	3.4.1.1, 3.5.1.3, 4.2.6.1
9	**Calculation of costs and integration evidence on time on treatment**	4.4.2.1
10	**The proportion of patients who receive subsequent treatment with gilteritinib**	4.4.2.1
11	**Other technical and consistency issues**	4.2.6.2

1.1 Overview of key model outcomes

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- The EAG prefers to use simplified model structure where a nested partition survival model (PSM) is used to reflect outcomes following second-line treatment.
- When using the nested PSM, the EAG also prefers to allow cure in second line setting and to also use the PSM to model outcomes in patients who relapse following haematopoietic stem cell transplantation (HSCT)
- The EAG prefers to use a revised and simplified version of the induction health state
- The EAG prefers to model a QuANTUM-First population
- The EAG prefers to use the multilevel network meta-regression (ML-NMR) to inform relative treatment effects in the model
- The EAG prefers to directly use the QuANTUM-First to inform outcomes in the standard chemotherapy and quizartinib arms of the model
- The EAG prefers to assume that mortality rates following complete composite remission (CRc) will be equivalent for quizartinib and midostaurin
- The EAG prefers to use time varying hazard ratios to model rates of relapse following haematopoietic stem cell transplantation.

- The EAG prefers to use the generalised gamma to model relapse from CRc and the Gompertz for overall survival (OS) from CRc
- The EAG prefers to use utility values from the QuANTUM-First trial where these are available
- The EAG prefers to assume that 90% of patients will receive gilteritinib as a second-line treatment regardless of first line treatment received
- NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost-effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained compared to other treatment options.

Overall, the technology is modelled to affect QALYs by:

- Increasing relapse-free survival
- Increasing overall survival

Overall, the technology is modelled to affect costs by

- Higher first-line treatment costs
- Lower subsequent treatment costs

The modelling assumptions that have the greatest effect on the ICER are:

- The population modelled: QuANTUM-First vs RATIFY
- How relative treatment effects are informed: MAIC vs MLNMR vs AMLSG 16-10 trial
- How outcomes in the standard care arm are informed: hazard ratio vs QuANTUM-First trial data

1.2 The decision problem: summary of the EAG's key issues

The company's decision problem excluded a key comparator (sorafenib) in the post-HSCT maintenance setting. Following a request for clarification from the EAG, the company included evidence for this comparator in an additional indirect comparison and in scenario analyses. This is discussed under Key Issue 5.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 No robust evidence of improved efficacy of quizartinib compared to midostaurin across all treatment phases

Report section	Sections 3.4.1, 3.5.1
Description of issue and why the EAG has identified it as important	In the absence of direct evidence comparing quizartinib + standard chemotherapy and midostaurin + standard chemotherapy, the company have conducted population-adjusted indirect treatment comparisons (ITCs). The company have not provided robust evidence of any efficacy advantage in terms of overall survival (OS), complete remission (CR) or cumulative incidence of response (CIR) for quizartinib over midostaurin. Further details of the separate technical issues which contribute to this key issue are described in Issue 2, Issue 3, and Issue 4. Relative effect estimates calculated using MAICs have been estimated within the FLT3-ITD+ subgroup of RATIFY trial of midostaurin, which is not reflective of the target population for decision making (see Issue 3). To overcome this limitation of MAICs, the company conducted ML-NMR, which provides flexibility to generate population averaged estimates which are applicable to any specified target population. Results of ML-NMRs of the QuANTUM-First ITT population and the RATIFY *FLT3-ITD*+ subgroup indicate no OS difference between quizartinib and midostaurin (HR [redacted], 95% CI: [redacted]) and a numerical advantage for midostaurin over quizartinib for CR (OR [redacted], 95% CI: [redacted]). Naïve comparisons support these results. While ML-NMR results indicate a statistically significant advantage for quizartinib over midostaurin for CIR following CR (HR [redacted], 95% CI: [redacted]), these results are biased due to imbalances in the non-randomised groups achieving CR in the QuANTUM-First trial, and adjustment for aggregate level covariates of all *FLT3-ITD*+ patients at baseline rather than those who achieved CR from the RATIFY trial.
What alternative approach has the EAG suggested?	The EAG considers that results of the MAICs, used within the company model base case, are not suitable for decision making. The EAG considers that the ML-NMR results reflect a population which is potentially suitable for decision making, if applied correctly within the economic model (see Issue 4). The EAG considers that bias in the population-adjusted ITCs of CIR is unresolvable due to the lack of published baseline characteristics of *FLT3-ITD*+ patients who achieved CR in the RATIFY trial.
What is the expected effect on the cost-effectiveness estimates?	The significant uncertainties associated with the ITC impact significantly on the cost-effectiveness model. Even if technical issues are addressed fundamental question remain regarding the inferences that can be drawn from these analyses, also see issue 6.
What additional evidence or analyses might help to resolve this key issue?	As requested during clarification, the EAG considers that an ITC of the QuANTUM-First trial and the AMGSL 16-10 trial of midostaurin may provide additional supportive evidence to address some of the limitations and uncertainty in the company ITCs including the RATIFY trial (see Issue 2). The EAG has performed a naïve comparison using published data from the QuANTUM-First trial and the AMGSL 16-10 trial but considers that a population-adjusted ITC using IPD from the QuANTUM-First trial may be more robust and informative. However, the EAG acknowledges that any ITC of the QuANTUM-First AMGSL 16-10 trials would also be associated with limitations, so this issue cannot be fully resolved.

Abbreviations: CIR: cumulative incidence of relapse; CR: complete remission; *FLT3-ITD*+: FMS-like tyrosine kinase 3 internal tandem duplication positive; IPD: individual patient data; ITC: indirect treatment comparison; ITT: intention to treat; MAIC: matching adjusted indirect comparison; ML-NMR: multilevel network meta-regression

Issue 2 Comparability of the QuANTUM-First and RATIFY trials

Report section	Section 3.4.1
Description of issue and why the EAG has identified it as important	Differences in trial design and outcome data between the QuANTUM-First and RATIFY trials impact upon the interpretation of the ITCs results and their generalisability to NHS clinical practice: • Differences in time frame between QuANTUM-First (2016 to 2021) and RATIFY (2008 to 2016) trials and improvements in clinical practice over time that cannot be adjusted for in the ITC. • Differences in age eligibility criteria in the QuANTUM-First (18 to 75 years) and RATIFY (18 to 59 years) trials. • Lack of comparable data on a number of treatment effect modifiers across the two trials limits which characteristics can be adjusted for in population-adjusted ITCs. • The composite complete remission (CRc) rate [CR or CRi], which is used to measure response in induction therapy in NHS practice, was only collected in the QuANTUM-First trial. ITCs could only be performed using CR rates, which were collected in both trials. • Differences in HSCT rates across the two trials and lack of adjustment for HSCT in the ITCs of OS and CIR
What alternative approach has the EAG suggested?	The EAG considers that these key differences in trial design and outcome data cannot be adjusted for and there for this issue cannot be resolved in the ITCs of quizartinib and midostaurin using the QuANTUM-First and RATIFY trials.
What is the expected effect on the cost-effectiveness estimates?	It is unclear how these uncertainties will impact on the ICER but it is likely to be highly sensitive to alternative inputs.
What additional evidence or analyses might help to resolve this key issue?	As requested during clarification, the EAG considers that an ITC of the QuANTUM-First trial and the AMGSL 16-10 trial of midostaurin may provide additional supportive evidence to address some of the limitations and uncertainty in the company ITCs including the RATIFY trial. The EAG has performed a naïve comparison using published data from the QuANTUM-First trial and the AMGSL 16-10 trial but considers that a population-adjusted ITC using IPD from the QuANTUM-First trial would be more informative. However, as above, the EAG acknowledges that any ITC of the QuANTUM-First AMGSL 16-10 trials would also be associated with limitations, so this issue cannot be fully resolved.

Abbreviations: CIR: cumulative incidence of relapse; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; *FLT3-ITD*+: FMS-like tyrosine kinase 3 internal tandem duplication positive; HSCT: Hematopoietic stem cell transplantation (allogeneic); ICER: incremental cost-effectiveness ratio IPD: individual patient data; ITC: indirect treatment comparison; ITT: intention to treat; MAIC: matching adjusted indirect comparison; ML-NMR: multilevel network meta-regression

Issue 3 Company MAICs do not reflect the correct target population for decision making

Report section	Sections 3.4.1
Description of issue and why the EAG has identified it as important	Clinical advice to both the company and the EAG is that the QuANTUM-First ITT population is more representative than the RATIFY trial population of the NHS population who would be eligible for treatment with quizartinib. Relative effect estimates calculated using MAICs have been estimated within the *FLT3-ITD+* subgroup of RATIFY trial of midostaurin, which is not representative of the target population for decision making. The effect estimates calculated in the MAICs cannot be applied to different populations, i.e., the target population in an NHS setting, and are therefore not suitable for decision making.
What alternative approach has the EAG suggested?	The EAG considers that the ML-NMR results reflect a population which is suitable for decision making, if applied correctly within the economic model (see Issue 4). The EAG considers that bias in the population-adjusted ITCs (i.e. MAICs and ML-NMRs) of CIR is unresolvable due to the lack of published baseline characteristics of *FLT3-ITD+* patients who achieved CR in the RATIFY trial.
What is the expected effect on the cost-effectiveness estimates?	Using the MLNMR to inform treatment effects increases the fully incremental ICER for quizartinib to £4,772 per QALY. However, due to the way in which the results of re MLNMR are used in the model this is likely to overestimate the effectiveness of quizartinib.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence required. An analysis which applies the results of ML-NMRs correctly within the economic model may partially resolve the issue (also see Issue 4)

Abbreviations: CIR: cumulative incidence of relapse; *FLT3-ITD+*: FMS-like tyrosine kinase 3 internal tandem duplication positive; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; MAIC: matching adjusted indirect comparison; ML-NMR: multilevel network meta-regression; SC standard chemotherapy

Issue 4 Incorrect application of population-adjusted ITC results in the economic model

Report section	Section 3.4.1.1
Description of issue and why the EAG has identified it as important	The company MAIC and ML-NMR approaches estimate different types of population-average treatment effects (marginal and conditional treatment effects respectively). The different interpretation of population-average treatment effects means that they must be applied appropriately for economic modelling. The company approach of applying a conditional HR from an ML-NMR to a baseline KM curve which is unadjusted for the treatment effect modifying covariates of interest results in aggregation bias. Furthermore, the use of population-adjusted ITC methods (i.e. MAIC or ML-NMR) is motivated by the existence of covariate effects. However, when covariate effects are present (prognostic or effect-modifying), hazards are mathematically non-proportional at a marginal level. Therefore, the company approach of fitting ITC models which require the proportional hazards (PH) assumption and applying the estimated constant HRs to baseline survival curves contradicts the assumed existence of covariate effects. This renders the population-adjusted ITCs unsuitable for decision making.
What alternative approach has the EAG suggested?	The EAG considers that this issue cannot be resolved with currently available evidence but suggests an additional analysis below which may resolve this issue.
What is the expected effect on the cost-effectiveness estimates?	The EAG has not be able to implement a correction to the economic model as it does not have access to the necessary data. In scenario analysis where the QuANTUM-First trial data is used directly in the model the full incremental ICER for quizartinib is £6,083 per QALY.
What additional evidence or analyses might help to resolve this key issue?	A correct approach to cost-effectiveness analysis while assuming the existence of covariate effects, would be to use the average survival curves for each treatment in the target population predicted within the ML-NMR directly within the economic model, rather than unadjusted baseline KM data, extrapolated using parametric survival modelling.

Abbreviations: EAG: Evidence Assessment Group; HR: hazard ratio, ITC: indirect treatment comparison; KM: Kaplan-Meier; ICER: incremental cost-effectiveness ratio; MAIC: matching adjusted indirect comparison; ML-NMR: multilevel network meta-regression; PH: proportional hazards; SC standard chemotherapy

Issue 5 No robust evidence of improved efficacy and safety of quizartinib in the post-HSCT maintenance setting

Report section	Sections 2.3, 3.2, 3.2.4
Description of issue and why the EAG has identified it as important	QuANTUM-First was not designed to estimate the efficacy and safety of separate phases of quizartinib therapy. Whilst QuANTUM-First provides evidence informing response and safety outcomes in the induction phase of treatment, the separate, relative effectiveness and safety of quizartinib against placebo in the consolidation and maintenance settings is uncertain and may be confounded by the efficacy and safety of prior treatment phases. In addition, sorafenib is a commonly used, off-licence and off-patent treatment recommended for use by NHS England in the post-HSCT maintenance setting but is not an option in the company's decision problem nor in the company's base case. There is no head-to-head comparison between quizartinib and sorafenib in the post-HSCT maintenance setting. Following a clarification request from the EAG, the company provided an unanchored MAIC comparing OS outcomes for quizartinib and sorafenib in the post-HSCT maintenance setting, using data from QuANTUM-First and the SORMAIN trial and incorporated results for OS into a scenario analysis for the economic model. The MAIC showed [redacted] that quizartinib [redacted] to sorafenib (HR [redacted]). A naïve comparison provided very similar results. The EAG found that the MAIC results are uncertain due to a number of significant limitations, namely: • Lack of anchor and adjustment for all known treatment effect modifiers (TEMs). • Lack of evidence that the constant hazards assumption, on which MAIC relies, is met. • Lack of evidence for outcomes other than OS, notably relapse.
What alternative approach has the EAG suggested?	The EAG has not conduced additional analyses but suggests that the company provide an anchored MAIC (see below).
What is the expected effect on the cost-effectiveness estimates?	In scenarios where quizartinib and sorafenib are assumed to have equivalent efficacy in the post-HSCT setting the fully incremental ICER for quizartinib decreases to £3,347 per QALY.
What additional evidence or analyses might help to resolve this key issue?	An anchored MAIC of the QuANTUM-First and SORMAIN trials, supported by a naïve comparison, may be feasible by first adjusting imbalances in baseline characteristics of the quizartinib and placebo post-HSCT maintenance groups in QuANTUM-First (e.g. propensity score matching or covariate adjustment methods). This would also further explore the existence and impact of any population differences and covariate effects. An ITC of RFS comparing quizartinib and maintenance therapy post-HSCT is probably feasible and could inform a scenario analysis for the company's economic model. Whilst the EAG's suggested alternative approach may partially address some of these concerns, the design of the QuANTUM-First trial prevents this issue from being fully resolved. Evidence for the effectiveness and safety of sorafenib post-HSCT maintenance following induction/consolidation with midostaurin would also be informative but is currently lacking.

Abbreviations: EAG: Evidence Assessment Group; HR: hazard ratio, ITC: indirect treatment comparison; KM: Kaplan-Meier; MAIC: matching adjusted indirect comparison; ML-NMR: multilevel network meta-regression; PH: proportional hazards

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 6 Validity of model predictions

Report section	Section 4.2.2
Description of issue and why the EAG has identified it as important	The economic model predicts substantial LY and QALY gains for quizartinib relative to midostaurin, driven primarily by the treatment effect applied to relapse from CRc. However, this contradicts results from both the company's MAIC and ML-NMR of OS, which show no evidence of a survival benefit in favour of quizartinib. These results are difficult to reconcile with the model predictions and are entirely a consequence of the selected modelling approach, which relies on surrogate relationships between intermediate outcomes and OS. The company's base case position requires dismissing the OS results from the ITC while simultaneously accepting the corresponding ITC results for relapse and assuming that relapse is an appropriate surrogate for OS. While the EAG considers the surrogate relationships implied by the economic model plausible, there are fundamental questions about the validity of the model predictions.
What alternative approach has the EAG suggested?	No alternative approach is necessary. The economic model could be revised to adopt a PSM approach which would allow better integration of the evidence on OS. However, this would likely create other issues that are equally intractable.
What is the expected effect on the cost-effectiveness estimates?	The result of the ITC of OS suggests that the economic model may be exaggerating the clinical benefits associated with quizartinib. Reducing the LY and QALY gains associated with quizartinib will increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	It is not possible to resolve this issue given the available clinical evidence.

Abbreviations: CRc: composite complete remission; EAG: Evidence Assessment Group; HR: hazard ratio, ICER: incremental cost-effectiveness ratio ITC: indirect treatment comparison; LY: life year MAIC: matching adjusted indirect comparison; ML-NMR: multilevel network meta-regression; OS: overall survival; PH: proportional hazards; PSM: partitioned survival model; QALY: quality adjusted life year

Issue 7 Appropriateness of using a state transition model to evaluate second-line treatment/modelling of induction health state

Report section	Section 4.2.2 and 4.2.6
Description of issue and why the EAG has identified it as important	Following criticism in TA523 for using a partitioned survival model (PSM), the company adopted a state transition model (STM) approach. The EAG considers this approach valid but is concerned that the company's modelling of second-line treatment is overly complicated and does not accurately reflect the supporting clinical evidence. Additionally, it does not allow the model to account for the possibility that patients may achieve a cure following second-line treatment. The EAG is also unclear why the company has used a different approach to model outcomes in a post-HSCT relapse setting to that used to model outcomes in patients who relapse without HSCT and considers this an important limitation of the company's base case model structure. The EAG is also concerned that the model does not appropriately integrate the evidence from the ITC of CR. Within the economic analysis, the OR from this analysis drive the proportion of patients who receive a second round of induction therapy rather than the overall rate of remission. Applying treatment effects in this manner does not align with the original purpose of the ITC analyses, which is to compare the overall rates of CR.
What alternative approach has the EAG suggested?	The EAG proposes retaining the STM structure to model outcomes following first-line treatment but favours using a nested PSM model to reflect outcomes in the second-line setting. This allows for more direct use of the available trial evidence (ADMIRAL trial) and allows cure to be modelled in a second-line setting. The EAG also favours using the PSM to model outcomes for patients who relapse following HSCT. The EAG favours reconfiguring the induction health state to better integrate the evidence from the ITC so that it directly determines the proportion of patients who achieve remission.
What is the expected effect on the cost-effectiveness estimates?	The fully incremental ICER for quizartinib decreases to £1,773 per QALY.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers the technical changes suggested to be unambiguous improvements on the company's base case model and that they largely resolve these issues.

Abbreviations: CR: complete remission; EAG: Evidence Assessment Group; HSCT: haematopoietic stem cell transplantation; ICER: incremental cost-effectiveness ratio ITC: indirect treatment comparison; LY: life year; OR: odds ratio; PSM: partitioned survival model; QALY: quality adjusted life year; STM: state transition model

Issue 8 Inconsistency between modelled outcomes and outcomes evaluated in ITC

Report section	Section 3.4.1.1, Section 3.5.1.3, Section 4.2.6.1
Description of issue and why the EAG has identified it as important	Relative treatment effects applied in the economic model are drawn from four ITCs that consider CR, OS (from the time of randomization), CIR, and OS following HSCT (scenario analysis only). These are respectively used to model: • The proportion of patients achieving CRc in the induction period • The rate of relapse following CRc • Mortality in patients who achieve CRc • Mortality in patients who receive an HSCT In all four cases, the outcome evaluated in the ITC differs from the outcome that is modelled. Regarding CR and CIR, the EAG considers the company's approach unavoidable given the available data. However, it is unclear if it is appropriate to transpose relative treatment effects in this way, and doing so substantially increases uncertainty in the predicted cost-effectiveness estimates. Regarding OS (from the time of randomization) and OS following HSCT, the EAG considers it inappropriate to apply the results of the ITC in this manner, as the outcomes being considered in the economic analysis fundamentally differ from those considered in the ITC.
What alternative approach has the EAG suggested?	The EAG recognizes that available data imposes limitations on what can be evaluated in the ITCs. The assumptions made regarding CR and CIR are therefore necessary if a treatment effect is to be modelled. Regarding OS, the EAG favours assuming that mortality in patients who achieve CRc is the same for both quizartinib and midostaurin. The EAG does not consider it possible or appropriate to inform this transition using data from the ITC of OS from time of randomisation. Additionally, the EAG does not consider it feasible to integrate the evidence from the ITC of OS following HSCT.
What is the expected effect on the cost-effectiveness estimates?	It is largely unclear how this issue impacts model results.
What additional evidence or analyses might help to resolve this key issue?	This issue is not fully resolvable given the data available. The changes suggested by the EAG offer a reasonable approach to modelling mortality following CRc.

Abbreviations: CIR: Cumulative incidence of relapse CR: complete remission; CRc: composite complete remission; EAG: Evidence Assessment Group; HR: hazard ratio, HSCT: haematopoietic stem cell transplantation; ICER: incremental cost-effectiveness ratio ITC: indirect treatment comparison; OS: overall survival

Issue 9 Calculation of costs and integration evidence on time on treatment

Report section	Section 4.4.2.1
Description of issue and why the EAG has identified it as important	Due to incomplete trial follow-up in the QuANTUM-First trial, the modelled time on treatment is calculated using a restricted mean. This method underestimates time on treatment and consequently underestimates drug acquisition, administration, and monitoring costs. The company's approach to calculating drug acquisition, administration, and monitoring costs also double-counts the impact of relapse, HSCT, and OS events when estimating time on treatment using both state occupancy and an uncensored time on treatment cure to determine whether costs should be applied. This approach will again significantly underestimate drug acquisition, administration, and monitoring costs, particularly those associated with quizartinib maintenance treatment.
What alternative approach has the EAG suggested?	The EAG recommends separate modelling approaches for time on treatment across the induction, consolidation, and maintenance phases: • Induction: Use state occupancy to determine the proportion of patients receiving treatment across all arms. • Consolidation: Apply lump sum costs upon entry to health states using the mean treatment duration observed in the trial for quizartinib and SC. Assume the same (mean) time on treatment for midostaurin as quizartinib. • Maintenance without HSCT: Use the relevant time on treatment from the trial for quizartinib and assume the same for midostaurin but use a truncated survival curve to reflect the SmPC.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that the company's approach to integrating the time on treatment evidence is very likely to underestimate the drug acquisition costs associated with quizartinib, particularly in the maintenance setting. The ICERs in the company's analysis are therefore likely to be underestimates.
What additional evidence or analyses might help to resolve this key issue?	The EAG is unable to implement its recommended approach within the economic model as it does not have access to all the necessary data.

Abbreviations: EAG: Evidence Assessment Group; ICER: incremental cost-effectiveness ratio; OS: overall survival; SC: standard care; SmPC: Summary of product characteristics

Issue 10 The proportion of patients who receive subsequent treatment with gilteritinib

Report section	Section 4.4.2.1
Description of issue and why the EAG has identified it as important	The company models the distribution of subsequent treatment (gilteritinib and FLAG-Ida) based on whether a 1st or 2nd generation FLT3 inhibitor is received in 1L. Clinical advice to the EAG suggests that this assumption underestimates the proportion of patients who receive subsequent treatment with gilteritinib in practice.
What alternative approach has the EAG suggested?	The EAG opts to use a higher proportion of patients to model gilteritinib based on clinical advice.
What is the expected effect on the cost-effectiveness estimates?	The fully incremental ICER for quizartinib decreases to £3,352 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further clinical input would help clarify how subsequent treatments are likely to be used should quizartinib be made available on the NHS.

Abbreviations: EAG: Evidence Assessment Group; FLAG-Ida: Fludarabine, cytarabine, idarubicin and granulocyte colony stimulating factor; FLT3: FMS-like tyrosine kinase 3 (refers to the protein)

Issue 11 Other technical and consistency issues

Report section	Section 4.2.6.2
Description of issue and why the EAG has identified it as important	The EAG identified several more minor issues regarding the parametrization of the economic model. These include: • The company's approach to extrapolating the observed survival data for relapse following CRc, OS following CRc, and OS following HSCT. • The utility set used in the economic model is informed by published values when values are available from the QuANTUM-First trial. It is also unclear if the values provided at clarification have been mapped to EQ-5D-3L. • Inconsistent approach to informing transition probabilities following HSCT, which uses a time-invariant approach for relapse and a time-varying approach for OS.
What alternative approach has the EAG suggested?	The EAG-preferred curves for modelling relapse from CRc are the generalized gamma for the 'RATIFY-like' population and the Gompertz for the unadjusted QuANTUM-First population. For OS from CRc, the EAG prefers the log-logistic curve for the 'RATIFY-like' population and the Gompertz for the unadjusted QuANTUM-First population. For OS following HSCT the EAG prefers to use the generalized gamma when modelling the 'RATIFY-like' population. The EAG prefers to use the utility set derived from the QuANTUM-First trial. To meet the requirements of the NICE reference case, these should be mapped to EQ-5D-3L if this has not already been done. Additionally, the EAG favours using time-invariant transition probabilities to model rates of relapse following HSCT.
What is the expected effect on the cost-effectiveness estimates?	Revising the extrapolations increases the fully incremental ICER for quizartinib to £3,498 per QALY. Revising the utility set decreases the fully incremental ICER for quizartinib to £3,431 per QALY. Revising the transition probabilities applied decreases the fully incremental ICER for quizartinib to £2,940 per QALY.
What additional evidence or analyses might help to resolve this key issue?	The changes implemented by the EAG largely resolve these issues. The company should map EQ-5D-5L values to EQ-5D-3L using the Hernández Alava mapping algorithm if this has not been done.

Abbreviations: CRc: composite complete remission; EAG: Evidence Assessment Group; EQ-5D-3L: EuroQoL-5D-3L; EQ-5D-5L: EuroQoL-5D-5L; HSCT: haematopoietic stem cell transplantation; OS: overall survival.

1.5 Summary of EAG's preferred assumptions and resulting ICER

The results of the EAG scenario analyses are summarised in Table 1 and Table 2. Table 1 uses the company's preferred model structure while Table 2 uses the EAG's preferred PSM structure. These results include the PAS discount for quizartinib only. Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

Table 1 EAG Exploratory fully incremental scenario analyses (deterministic)

	Scenario	Technology	Total		Incremental		Fully incremental ICER
			Costs	QALYs	Costs	QALYs	
	Company base case	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£47,175
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,459
1a	**PSM structure**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,994
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£311
1b	**PSM structure + 2L cure**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,478
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,773
1c	**Calculation errors**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£23, 526
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£18,000
2a	**QuANTUM-First population**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£55,937
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£4,220
2b	**2a + Induction reconfigured**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£61,324
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,843
2c	**2a + ML-NMR**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£140,509
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£4,272
2d	**2c+direct RFS and OS**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£176,732
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£6,083
2e	**2d+ AMLSG 16-10 trial of midostaurin**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£32,979
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2f	**2d+ preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£166,361
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,792
2g	**MAIC preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£101,755
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,498
3	**KM data for post-HSCT relapse**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£47,415
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£2,940
4	**QuANTUM-First HRQoL**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£46,374
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,431
5a	**Linking treatment effect**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£46,846

	to 2nd line therapy	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,432
5b	**Assuming 90% of patients receive gilteritinib**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£40,787
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,352
5c	**5a+5b**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£41,017
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,387
6a	**Sorafenib maintenance (mido+SC) HR 1**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£30,431
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,347
6b	**Sorafenib maintenance (mido+SC) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£30,117
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,431
7a	**Sorafenib maintenance (all) HR 1**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£12,958
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7b	**Sorafenib maintenance (all) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,731
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: = HR: hazard ratio; HRQoL: health-related quality of life; HSCT: allogeneic haematopoietic stem cell transplant; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; mido: midostaurin; ML-NMR: multilevel network meta-regression; OS: overall survival; PSM: partitioned survival model; QALY: quality-adjusted life-years; RFS: relapse-free survival; SC, standard chemotherapy; 2L: second line

Table 2 EAG Exploratory fully incremental scenario analyses on PSM structure (deterministic)

	Scenario	**Technology**	**Total**		**Incremental**		**Fully incremental ICER**
			Costs	**QALYs**	**Costs**	**QALYs**	
	Company base case	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£47,175
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,459
1a	**PSM structure**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,994
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£311
1b	**PSM structure + calculation errors**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£53,263
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£862
1c	**PSM structure + Cure (PSM model)**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,478
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,773
1d	**EAG preferred configuration of PSM**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,914
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£5,229
2a	**QuANTUM-First population**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£62,772

		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£537
2b	**2a + Induction reconfigured**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£20,281
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2c	**2a + ML-NMR**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£31,966
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2d	**2c+direct RFS and OS**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£277,872
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,059
2e	**2d+ AMLSG 16-10 trial of midostaurin**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£31,234
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2f	**2d+ preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£251,788
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,975
2g	**MAIC preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£117,696
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£183
3	**KM data for post-HSCT relapse**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£16,363
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
4	**QuANTUM-First HRQoL**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,059
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£309
5b	**Assuming 90% of patients receive gilteritinib**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£44,618
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,480
6a	**Sorafenib maintenance (mido+SC) HR 1**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,721
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
6b	**Sorafenib maintenance (mido+SC) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,965
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7a	**Sorafenib maintenance (all) HR 1**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£13,783
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7b	**Sorafenib maintenance (all) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,507
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: HR: hazard ratio; HRQoL: health-related quality of life; HSCT: allogeneic haematopoietic stem cell transplant; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; mido: midostaurin; ML-NMR: multilevel network meta-regression; OS: overall survival; PSM: partitioned survival model; QALY: quality-adjusted life-years; RFS: relapse-free survival; SC, standard chemotherapy; 2L: second line

Results for the EAG's preferred base case are reported in Table 3. The EAG base case incorporates the following scenarios:

Scenario 1a: PSM structure

Scenario 1b: PSM structure + calculation errors

Scenario 1c: PSM structure + Cure

Scenario 1d: EAG preferred configuration of PSM

Scenario 2b: 2a + Induction reconfigured

Scenario 2f: 2d+ preferred extrapolations

Scenario 3: KM data for post HSCT relapse

Scenario 4: QuANTUM-First HRQL

Scenario 5b: Assuming 90% of patients receive subsequent treatment with gilteritinib

Table 3 EAG's preferred base case (fully incremental deterministic results)

Scenario	Technology	Total		Incremental		Fully incremental ICER
		Costs	QALYs	Costs	QALYs	
EAG-corrected company base-case (PSM)	SC regimen	[redacted]	[redacted]			
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£133,861
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,288

Abbreviations: EAG: evidence assessment group; ICER: incremental cost-effectiveness ratio; PSM: partitioned survival model; QALY: quality-adjusted life-years; SC: standard chemotherapy

EXTERNAL ASSESSMENT GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of the company's submission (CS) to NICE from Daiichi Sankyo on the clinical effectiveness and cost effectiveness of quizartinib (Vanflyta®) for treating people with newly diagnosed acute myeloid leukaemia (AML) that is Feline McDonough sarcoma (FMS)-like tyrosine kinase 3 internal tandem duplication positive (*FLT3-ITD*+). The version of the CS appraised in this report is v4.0 (dated 05042024), which supersedes versions previously submitted by the company between November 2023 and April 2024 and addresses a number of issues previously raised by the EAG and NICE.

In July 2023, the Food and Drug Administration (FDA) approved quizartinib with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed *FLT3-ITD*+ AML. The FDA did not licence quizartinib as maintenance monotherapy following allogeneic haematopoietic stem cell transplantation (HSCT), as improvement in overall survival (OS) with quizartinib "has not been demonstrated in this setting."[1]

Quizartinib received a full marketing authorisation throughout the EU granted by the European Medicines Agency (EMA) in November 2023.[2] Quizartinib is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib single-agent (monotherapy) maintenance therapy for adult patients with newly diagnosed AML that is *FLT3-ITD*+. In March 2024, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a full marketing authorisation for quizartinib for the same indication.[3] Unlike the FDA, the EMA and MHRA authorised the use of quizartinib monotherapy in the post-HSCT maintenance treatment setting. The proposed indication within the company submission covers the full EMA and MHRA marketing authorisations.

2.2 Background

2.2.1 Disease background

The company's description of AML is reported in CS, Document B, Section 1.3, and is broadly appropriate and relevant to the decision problem.

AML is a haematological cancer of the blood and bone marrow, characterised by the overproduction of early immature myeloid cells (blasts). It is the most common haematological cancer, yet a rare form of cancer, accounting for less than 1% of all new cancer cases and 2% of cancer deaths in the UK.[4] In 2016-2018 and 2017-2019 respectively, 3,089 new cases and 2,678 deaths related to AML were reported in the UK. Incidence of AML increases with age, with over 70% of new cases being in individuals over 60 years of age. Incidence rates and mortality rates are highest in people aged 85 to 89 years; around 42% of new cases are diagnosed in people aged 75 years and above between 2016 and 2018.[4]

The outcome of patients with AML is poor, with a five-year survival of 33.6% overall, although survival varies substantially depending on age and rapidly declines with increasing age at diagnosis. [4, 5] Survival is influenced by disease-specific factors (including cytogenetic and/or molecular genetic alterations, including *FLT3*, nucleophosmin 1 [*NPM1*]) and patient-specific variables including age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), organ function, and other comorbidities.[6] Age is the most important patient-specific risk factor, while chromosomal aberrations/genetic mutations have been considered the most prominent disease-specific risk factors.[7] Performance status, general health, and specific comorbidities modulate the impact of age on tolerance to chemotherapy, whereas specific age-related AML-associated genetic abnormalities increase the risk of resistance to treatment.[6] Testing for genetic mutations, including *FLT3*, has become increasingly important for risk assessment and in informing the treatment of AML.[6, 8]

FLT3 is one of the most common AML mutations.[9 10] There are two types of *FLT3* mutations: *FLT3* internal tandem duplications (*FLT3-ITD*) and point mutations or deletion in the tyrosine kinase domain (*FLT3-TKD*). The *FLT3-ITD* mutation is found in 20 to 25% of AML patients, and is more common than the *FLT3-TKD* mutation, which occurs in 7% to 10% of all AML cases.[11-14] The incidence of *FLT3-ITD* mutations decreases with age, up to 35% in patients between 20 and 59 years compared with 16% to 20% in older patients.[14-16] The *FLT3-ITD* mutations are associated with a high leukaemic burden with marked leukocytosis and a high rate of blasts. The *FLT3-ITD* mutation is associated with a relatively poor prognosis, with relapse being the principal cause of treatment failure. Approximately 75% of patients with *FLT3-ITD*+ AML at diagnosis continue to have the ITD mutation at relapse.[17]

2.2.2 Quizartinib

The EAG considers the company's description of the technology to be clear and broadly appropriate. Quizartinib is an oral small molecule receptor tyrosine kinase (RTK) inhibitor of FMS-like tyrosine kinase 3 (*FLT3*) signalling, which targets *FLT3-ITD* mutations.

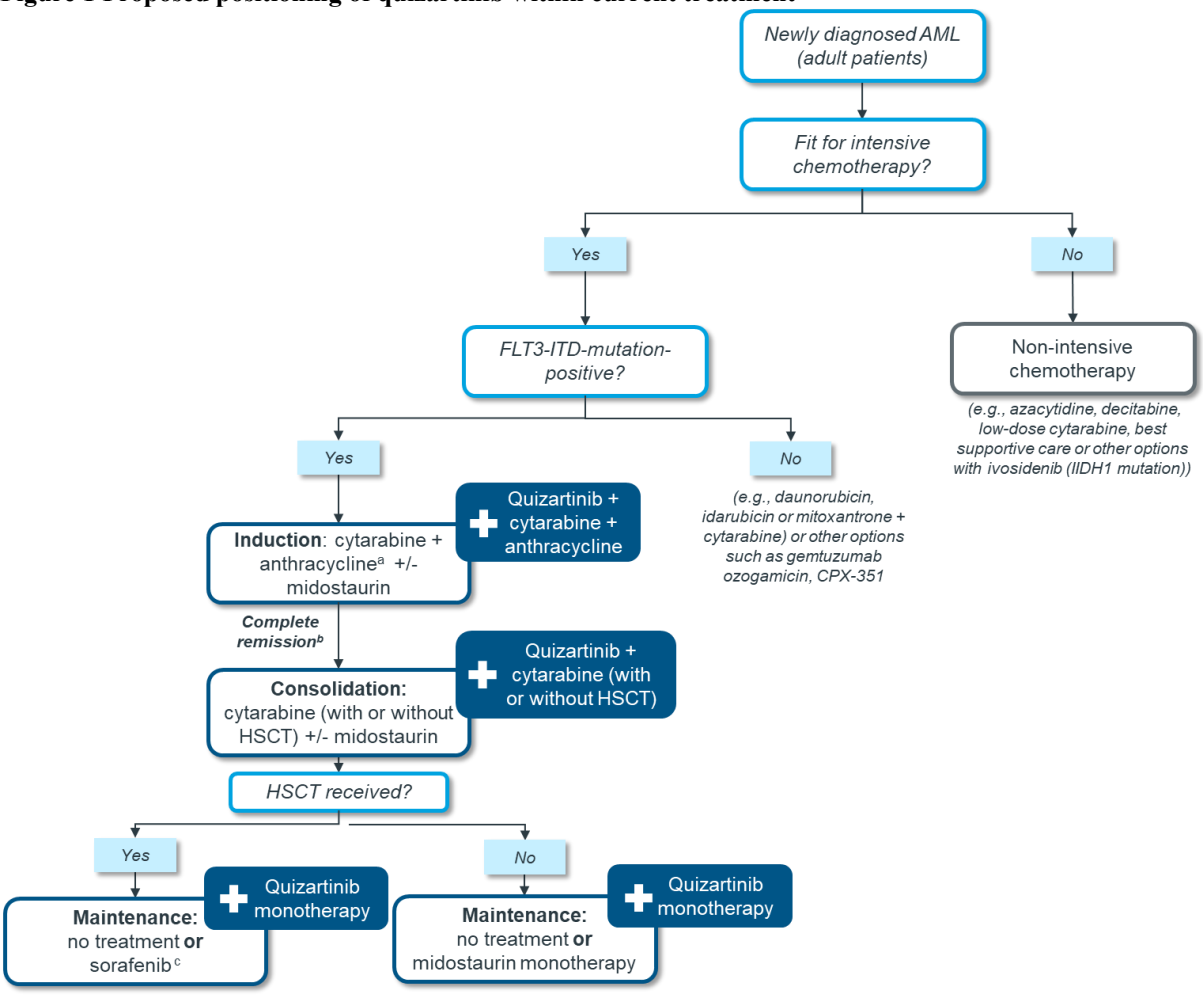
Quizartinib is supplied as oral tablets and is administered in combination with standard chemotherapy (daunorubicin or idarubicin + cytarabine) at a dose of 35.4 mg (2 × 17.7 mg) once daily for two weeks during each cycle of induction (hereafter referred to as quizartinib induction therapy). Patients may receive up to two cycles of induction. For patients who achieve complete remission (CR) or complete remission with incomplete haematologic recovery (CRi), quizartinib is given at 35.4 mg once daily for two weeks in each cycle of consolidation chemotherapy (up to four cycles) alongside standard cytarabine therapy, followed by quizartinib single-agent maintenance therapy at 26.5 mg once daily (hereafter referred to as quizartinib consolidation therapy). After two weeks, if the QT interval (the interval between the start of the Q wave and the end of the T wave) corrected by Fridericia's formula (QTcF) is ≤ 450 milliseconds (ms), the maintenance dose is increased to 53 mg (2 × 26.5 mg) once daily. Single-agent maintenance therapy may be continued for up to 36 cycles (hereafter referred to as quizartinib maintenance therapy). For patients who proceed to HSCT, quizartinib should be stopped seven days prior to initiating a conditioning regimen and may be resumed after completion of the transplant based on white blood cell (WBC) count and at the discretion of the treating physician for individuals with sufficient haematologic recovery and with ≤ Grade 2 graft-versus-host disease (GVHD), not requiring the initiation of new systemic GVHD therapy within 21 days.

Unlike type I inhibitors (such as midostaurin) which target both ITD and TKD mutations, quizartinib is a type II inhibitor which are only active in cells with *FLT3-ITD*, but not *FLT3* kinase domain point mutations.[18] The company argue that the additional selectivity of quizartinib may limit off-target effects and could reduce the drug toxicity and adverse effects to patients associated with first-generation inhibitors. As discussed in Section 3.4.1, the EAG believes that, as the company did not provide evidence comparing the relative safety and tolerability of quizartinib compared with midostaurin, the validity of this claim of reduced drug toxicity and adverse events remains uncertain..

2.2.3 Treatment pathway

Figure 1 summarises the current treatment pathway for AML patients in England and Wales, and the company's proposed positioning of quizartinib. The company positioned quizartinib within the treatment pathway for newly diagnosed *FLT3-ITD*+ in combination with standard cytarabine and anthracycline induction therapy, quizartinib in combination with standard cytarabine consolidation chemotherapy (with or without HSCT), and quizartinib as single-agent maintenance therapy with or without prior HSCT, which is in line with the full EMA and MHRA marketing authorisations. Following a request for clarification, the company updated the post-HSCT maintenance treatment pathway by including sorafenib, which NHS England has recommended in this setting since November 2023.[19] Overall, the EAG considers the company's updated description of the treatment pathway for newly diagnosed *FLT3-ITD*+ AML broadly appropriate.

Figure 1 Proposed positioning of quizartinib within current treatment



Source: Response to clarification questions part 1, Figure 26
Abbreviations: AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase 3; HSCT, haematopoietic stem cell transplant; ITD, internal tandem duplication.
Notes: a. In the NHS Pan London guidelines daunorubicin is recommended whereas in the ELN guidelines either daunorubicin or idarubicin are recommended b. complete remission or complete remission with incomplete haematologic recovery. c. sorafenib is recommended by NHS England since November 2023

2.2.3.1 Induction and consolidation setting

The aim of treatment for newly diagnosed AML is cure. For people who are fit enough to undergo intensive treatment, induction chemotherapy is initially administered to achieve a remission. After remission, further cycles of chemotherapy are given to reduce the risk of disease recurrence (consolidation therapy). The standard approach for adults with newly diagnosed AML who are considered fit for intensive chemotherapy is to undergo genetic testing. *FLT3*-mutation-positive patients are eligible for midostaurin therapy, which targets both ITD and TKD mutations.[20] Midostaurin is the only FLT3 inhibitor currently recommended in the first line treatment of *FLT3* mutation positive AML patients for induction and consolidation therapy. [21-23] It is the primary and most relevant comparator to quizartinib, and intensive chemotherapy alone is rarely used in practice in this population. As induction therapy, midostaurin is administered with standard daunorubicin and cytarabine. Clinical advice to the EAG indicated that, in the UK, the standard of care includes two

induction courses (one course, followed by count recovery and a subsequent induction course). For patients who achieve a CR, midostaurin is administered with high-dose cytarabine as consolidation therapy. Clinical advice to the EAG indicated that consolidation therapy is normally delivered in the UK in one to two cycles. Patients in remission and sufficiently fit may be eligible for allogeneic HSCT, provided a suitable donor is identified. Clinical advice to the EAG indicated that assessment of minimal residual disease (MRD) is a key factor influencing decisions to proceed to HSCT in the UK. For patients who achieve CR after the second induction cycle and are MRD-positive, HSCT is considered for those who are sufficiently fit. Conversely, for MRD-negative patients, prognosis is highly favourable and HSCT is not typically recommended, as it does not significantly improve outcomes. European LeukemiaNet (ELN) recommend consolidation with allogeneic HSCT as the preferred post-remission option for patients with an estimated relapse risk exceeding 35% to 40%.[23, 24]

2.2.3.2 Maintenance setting

Midostaurin is also recommended within TA523 as maintenance monotherapy following induction and consolidation.[21, 23, 25] Sorafenib, a type II TKI inhibitor is recommended by ELN guidelines and is available as a routine treatment option via a NHS England clinical commissioning policy (published November 2023) for maintenance therapy in adults with *FLT3-ITD* AML following HSCT.[19] Clinical advice to the EAG indicated that sorafenib is now widely used in the NHS and prescribed to most *FLT3-ITD*+ patients after HSCT.

Following a request for clarification from the EAG, the company added sorafenib to the maintenance pathway following HSCT. This is reflected in Figure 1.

2.2.3.3 Relapse/refractory setting

Clinical advice to the EAG indicated that most individuals under 70 years old will receive a second-line salvage therapy in the relapsed or refractory setting, where the therapeutic aim remains cure. Genetic testing is required to confirm that *FLT3*-mutation-positivity remains, as *FLT3* mutation may disappear and become wild-type *FLT3* in a minority of patients in this setting. For patients with a confirmed *FLT3*-mutation, gilteritinib, a first-generation type I FLT3 inhibitor, will be prescribed in most cases, as per NICE TA642, [21] whilst a minority (<10%) may receive 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 may be offered intermediate-dose cytarabine regimen (IDAC), where the intention remains to cure patients. People who are not eligible to chemotherapy and a HSCT will require palliative treatment with intermittent hydroxycarbamide.

2.2.4 Unmet need

The company states that patients with newly diagnosed *FLT3-ITD*+ AML have a significant unmet need, due notably to the poor prognosis associated with the high risk of relapse within the first two

years following diagnosis, the relatively limited range of therapeutic options in this population, side effects and risk of relapse following established therapy including HSCT. Whilst the EAG agrees that treatment-related mortality and relapse in this population remain concerning, since the ELN 2017 guidelines for the diagnosis and management of AML in adults, a number of advances in diagnosis and therapies have occurred. This includes notably developments in genomics, MRD assessment techniques and their utility for assessing treatment response and disease risk, and the development of a novel agents and developments in HSCT. This means that the prognosis for AML with *FLT3*-ITD (without adverse-risk genetic lesions) has improved, irrespective of the *FLT3-ITD* allelic ratio or concurrent presence of NPM1 mutation.[6, 23]

2.3 Critique of company's definition of decision problem

CS Document B, Table 1 presents the decision problem, including a description of the final scope issued by NICE, the decision problem addressed within the submission and the rationale for any differences between the two. This information, along with the EAG comments on the rationale provided, is presented in Table 4 below.

The population in the CS is people with newly diagnosed AML that is *FLT3-ITD*+ and is aligned with the NICE scope. Quizartinib treatment is aligned with the NICE scope and its EMA and MHRA licence indications during the induction, consolidation and maintenance phases of treatment. However, QuANTUM-First was not designed to estimate the efficacy and safety of separate phases of quizartinib therapy. Whilst QuANTUM-First provides evidence informing response and safety outcomes in the induction phase of treatment, the separate, relative effectiveness and safety of quizartinib against placebo in the consolidation and maintenance settings is uncertain and may be confounded by the efficacy and safety of prior treatment phases. As mentioned in Section 2.1, the FDA opted to not licence quizartinib as a maintenance treatment following HSCT maintenance as its efficacy was not demonstrated in this setting. The evidence for quizartinib in the post-HSCT setting is further discussed in Sections 3.4.2 and 3.5.2.

The NICE scope included a non-exhaustive list of comparator therapies without quizartinib for all phases of treatment. The decision problem initially presented in the CS limited the choice of comparators to midostaurin for all treatment phases, which is delivered with daunorubicin + cytarabine at induction, with cytarabine chemotherapy during consolidation, and as a single agent during the maintenance phase for patients who achieve CR but did not receive HSCT. In addition, the company model analyses included intensive chemotherapy without midostaurin across all treatment phases, as it is still used in a minority of patients where midostaurin is deemed unsuitable (such as patients with severe gastrointestinal complications). EAG clinical advisers confirmed that limiting the choice of comparators to midostaurin in induction and consolidation phases was appropriate and that

the exclusion of other treatments listed in the NICE scope (mitoxantrone, etoposide, amsacrine and azacytidine) was appropriate for newly diagnosed *FLT3-ITD*+ AML who were fit for intensive chemotherapy.

In the post-HSCT maintenance setting the company omitted sorafenib as comparator. As discussed in Section 2.2.3.2, sorafenib is commonly used in clinical practice, and the EAG believe that it should be evaluated as a relevant comparator. In the company's response to clarification, the company agreed to add this comparator to the treatment pathway informing the decision problem. They also provided additional analysis comparing the effectiveness of quizartinib and sorafenib as post-HSCT maintenance therapies. This is further discussed in Sections 3.4.2 and 3.5.2.

The final scope issued by NICE listed people who are ineligible for HSCT as a subgroup to be assessed as part of the decision problem. However, the CS did not examine this subgroup in its decision problem. The company justified the decision due to the design of the main quizartinib trial, QuANTUM-First, a placebo-controlled randomised trial comparing quizartinib + standard chemotherapy against placebo + standard chemotherapy in newly diagnosed *FLT3-ITD*+ AML. The company stated that QuANTUM-First enrolled patients who were eligible for intensive chemotherapy, where the "ultimate therapeutic goal is HSCT"; this meant that people ineligible for HSCT were not a pre-specified subgroup in the trial, which precluded a separate analysis for this subset of patients. The EAG believe that the company's rationale is inappropriate, because eligibility to HSCT is not determined at the point of initiating intensive chemotherapy Clinical advice to the EAG indicated that in practice, eligibility to HSCT depends on whether the patient achieved a complete response following induction or consolidation, fitness status, the availability of a suitable donor, and MRD status. However, the EAG acknowledge that a subgroup analysis of patients who are not eligible to HSCT may not be informative to the broader decision problem due to the heterogeneity of this subpopulation. For instance, the prognosis of patients who do not receive HSCT due to lack of response to intensive chemotherapy is likely to differ significantly from that of patients who may not need HSCT following a deep response to chemotherapy with no MRD.

Table 4 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with newly diagnosed AML that is *FLT3-ITD+*	Aligned with NICE scope	NA	The CS only considers people with newly diagnosed AML that is FLT3-ITD+ who are fit for intensive chemotherapy. This is appropriate, as patients who are not eligible for intensive chemotherapy will not receive a FLT3 inhibitor.
Intervention	Quizartinib	Aligned with NICE scope **Induction phase**: Quizartinib + chemotherapy (daunorubicin or idarubicin + cytarabine) **Consolidation phase**: Quizartinib + chemotherapy (cytarabine) **Maintenance phase**: quizartinib single agent maintenance therapy for patients who achieve CR (with or without HSCT)	NA	The intervention described in the CS is in line with the NICE scope and its EMA / MHRA licenced indication.
Comparators	Induction phase: • Established clinical management without quizartinib, including but not limited to midostaurin with daunorubicin and cytarabine. Consolidation phase: • Established clinical management without quizartinib, including but not limited to midostaurin with cytarabine alone or in combination with other	**Induction phase**: Midostaurin + chemotherapy (daunorubicin + cytarabine) **Consolidation phase**: Midostaurin + chemotherapy (cytarabine) **Maintenance phase**: Midostaurin single agent maintenance therapy for patients who achieve CR but did not receive HSCT.	The non-routine chemotherapy treatments (mitoxantrone, etoposide, amsacrine) were not considered as appropriate comparators for the newly diagnosed AML patients with *FLT3-ITD+*. Azacitidine is not considered an appropriate comparator. Justifications for these exclusions are reported in CS, Document B, Table 1	The comparators described in the CS only include a subset of those that are included in the NICE scope. The EAG agree with the choice of comparator treatments during induction and consolidation phases. Clinical advisers to the EAG agree that the exclusion of mitoxantrone, etoposide, amsacrine and azacitidine is appropriate. The EAG disagrees with the exclusion of sorafenib as a comparator in the post-HSCT

	chemotherapy drugs, such as mitoxantrone, etoposide, or amsacrine.			maintenance treatment setting. Sorafenib is recommended by NHS England since November 2023 as a routine commissioning treatment option for adults with *FLT3-ITD+* AML undergoing allo-HSCT.[19] Clinical advice to the EAG confirmed that sorafenib is now widely used in this setting.
Outcomes	The outcome measures to be considered include: • Overall survival • Event-free survival • Relapse-free survival • Adverse effects of treatment • Health-related quality of life.	The outcome measures to be considered include: • Overall survival • Event-free survival • Relapse-free survival • Adverse effects of treatment • Health-related quality of life • Complete remission • Duration of complete remission • Transplantation rate	Consistent with TA523 and the endpoints collected in the QuANTUM-First trial, complete remission, duration of complete remission, and transplantation rate were also considered relevant outcomes.	The CS includes all outcomes listed in the NICE scope; the addition of complete remission, duration of complete remission and transplantation rate are relevant to the decision problem.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and	Aligned with NICE scope	NA	The economic analysis is conducted in line with the reference case, except for the utility set used in the model. See Table 14 for details. Confidential commercial arrangements for comparator treatments have not been accounted for in the company's analysis. The EAG presents analyses inclusive of these commercial arrangements in a confidential appendix to this report.

	cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups	People who are ineligible for HSCT	No subgroup was considered.	Based on the QuANTUM-First protocol, all patients enrolled in the trial were eligible for intensive chemotherapy where the ultimate therapeutic goal is HSCT. Therefore, a subgroup analysis of people ineligible for HSCT was not a pre-specified subgroup and such analysis could not be conducted due to the trial design.	The EAG believe that the company rationale for not considering the subgroup of patients who are ineligible for HSCT following chemotherapy is not appropriate. In practice, eligibility for HSCT is not determined at the point of initiating intensive chemotherapy. The exclusion of people unfit for intensive chemotherapy during trial enrolment does not preclude considering outcomes for people who are ineligible for HSCT after intensive therapy. The ultimate goal for intensive chemotherapy is newly diagnosed AML patients is cure, not HSCT. However, the EAG acknowledge that a subgroup analysis of patients who are not eligible to HSCT may not be informative to the broader decision problem due to the heterogeneity of this subpopulation.

Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	NA	NA	No further comments.

Abbreviations: *FLT3-ITD+* FMS-like tyrosine kinase 3 internal tandem duplication positive; NA: not applicable; EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency; HSCT: Hematopoietic stem cell transplantation; CS: Company submission; EAG: External Assessment Group; AML: Acute myeloid leukaemia

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant clinical evidence relating to the efficacy and safety of first-line treatment options in adults with newly diagnosed *FLT3-ITD*+ AML that is Details of the review are reported in Appendix D of the CS.

3.1.1 Searches

The search strategies to identify studies of quizartinib and comparators for patients with *FLT3*+ AML were included in Appendix D of the CS. These searches were used to identify evidence for the clinical evidence SLR and the indirect treatment comparison (ITC).

Some weaknesses were identified with the search approach taken which may have affected optimal retrieval of all relevant studies. These are detailed in Appendix Table 39. The EAG considered sorafenib to be a relevant comparator in the post-HSCT maintenance therapy phase, however this drug was not included in the search strategies presented in the CS. Therefore, some studies of sorafenib for patients with *FLT3*+ AML could have been missed by the searches presented.

3.1.2 Study Selection

The review eligibility criteria are reported in Appendix D, Table 1. Studies of adults with untreated *FLT3*+ AML were included. A list of eligible pharmacological treatments indicated for *FLT3*+ AML was provided. The list included relevant interventions (including midostaurin, daunorubin, and cytarabine), although it did not include sorafenib. Comparative trials, non-comparative trials and observational studies were eligible for inclusion. There were no restrictions by date or location, although non-English publications were excluded. All references were screened in duplicate, with disagreements resolved by a third reviewer. Reasons for exclusion were reported.

The selection criteria for the SLR were generally inclusive. However, the EAG considers that excluding studies of sorafenib from the systematic review was a significant limitation. As discussed in Section 2.2.3, sorafenib is recommended by NHS England and a commonly used treatment in the NHS as maintenance therapy in FLT3-*ITD*+ patients following HSCT; as such, it is a relevant comparator for this population.

The EAG also believes that excluding non-RCT evidence from the evidence synthesis was a limitation, given the limited generalisability of the RATIFY trial to inform the decision problem. This is further discussed in Section 3.3.1.1 and Section 3.3.1.2.

3.1.3 Data extraction

Data extraction was conducted by a single reviewer and validated by a second. Disagreements were resolved through discussion or arbitration by a third reviewer. Data extraction of outcome data was undertaken for the two RCTs that were included in the ITC. For all other studies, only design characteristics were extracted. Overall, the EAG believes that the data extraction process appeared generally appropriate.

3.1.4 Quality assessment

Two quality appraisal tools were used to assess the risk of bias for included studies. These tools were not described or named in the submitted documents but appear to be the Cochrane Risk of Bias 1.0 tool for RCTs and the ROBINS-I for the critical appraisal of observational (cohort) studies. Results were reported in embedded Microsoft Excel sheets and justifications for decisions were generally only reported for the RCTs. The CS did not specify the process for appraising the quality of the studies included in the systematic review. Despite the limited reporting, the EAG broadly agrees with the company's appraisal of the two RCTs (QuANTUM-First and RATIFY) used in the submission's ITC.

3.1.5 Evidence synthesis

Owing to the lack of direct comparison between quizartinib and midostaurin, an ITC was conducted. Two studies were included in this synthesis: QuANTUM-First (NCT02668653) and RATIFY (NCT00651261) trials. A summary and critique of these trials is presented in Sections 3.2 and 3.3 respectively. Sections 3.4 and 3.5 discuss and critique the ITC.

Following a request for clarification from the EAG, the company provided an indirect comparison between quizartinib and sorafenib in the subset of *FLT3-ITD*+ patients in the maintenance therapy setting following HSCT. This is further discussed in Section 3.3.2 and Section 3.4.2.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The company systematic review identified one RCT of quizartinib in newly diagnosed *FLT3*-ITD+ AML, QuANTUM-First. This section provides a summary and critique of this trial.

The methodology of the QuANTUM-First trial is summarised CS Document B, Table 5.

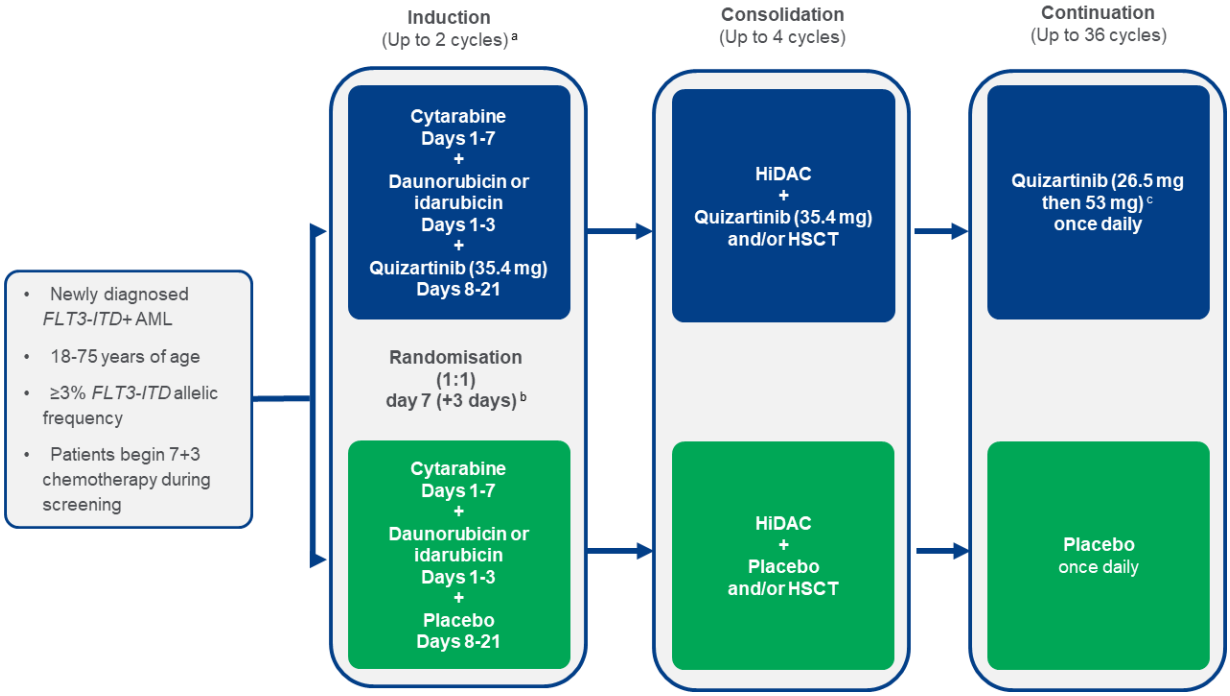
3.2.1 Trial design

QuANTUM-First was an international, phase 3, placebo-controlled, double-blind randomised trial that evaluated the efficacy and safety of quizartinib in patients with newly diagnosed *FLT3-ITD*+ AML. Starting in September 2016, 539 adult patients from 26 different countries were randomised 1:1 to

either quizartinib plus standard chemotherapy (SC) or placebo plus SC. SC therapy aligned with standard treatment paradigms consisting of cytarabine + anthracycline induction followed by cytarabine consolidation. Randomisation was stratified according to three criteria: region (North America, Europe, and Asia/other), age (<60 years, or ≥ 60 years), and WBC count at the time of AML diagnosis (<40 × 10^9/L, or ≥ 40 × 10^9/L).

The study design is represented schematically in Figure 2. The trial comprised three consecutive treatment phases. These included an induction, consolidation, and continuation (thereafter referred to as maintenance phase), as described in Section 2.2.2 of the CS. Additionally, the trial included a long-term follow-up phase, which began after patients had received quizartinib or placebo for 36 cycles in the maintenance phase or after permanent discontinuation of the study drug in any other phase.

Figure 2 Study design of the QuANTUM-First trial



Source: CS Document B, Figure 4

Abbreviations: HSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukaemia; *FLT3-ITD*, FMS-like tyrosine kinase 3-internal tandem duplication; HiDAC, high-dose cytarabine.

Notes: a. During Cycle 2 of the induction phase, investigators may have chosen to administer the "7 + 3" or the "5 + 2" chemotherapy regimen, and study drug would therefore have started on Day 8 or Day 6, respectively. b. Randomisation could be delayed to days 8 to 10 to address clinical concerns (e.g. electrolyte abnormalities, QT prolongation). c. The dose of study drug on Cycle 1 Days 1 to 15 was to be 26.5 mg orally once daily. On Cycle 1 Day 16, the dose was to be increased to 53 mg/day if the average QTcF of the triplicate ECG was ≤450 ms on Cycle 1 Day 15. Once the dose was increased to 53 mg/day, the subject was allowed to continue this dose as long as dose reduction was not needed.

Details of chemotherapy doses are included in Table 5 in Section 3.2 of Document B of the CS. Patients were not allowed to receive concomitant chemotherapy, immunotherapy, radiotherapy transplant or any ancillary therapy for AML that was not specified in the protocol, or that was considered investigational while they were on the study drug. Other prohibited drugs are listed in CS Document B, Table 5.

Patients who achieved and were still in CR or CRi (i.e., composite complete remission) were permitted to undergo allogeneic-HSCT after the induction phase, at any time during the consolidation phase, or within the first three months of the maintenance phase, if the following criteria were met:

- It is planned from the start of the consolidation phase that the patient will undergo HSCT as part of consolidation therapy;
- A donor was not found during the consolidation phase, but became available after the start of the maintenance phase;
- The investigator discusses the case with the medical monitor;
- Based on local laboratory results, there were confirmed <5% of blasts based on the most recent bone marrow aspirate;
- The transplant is performed within 3 months from the start of maintenance therapy.

The protocol specifies that patients should discontinue the study drug at least 7 days before the start of the conditioning regimen for HSCT. HSCT performed for any other reason outside of the above-listed criteria was considered non-protocol-specified AML therapy. Patients in receipt of non-protocol-specified AML therapy discontinued the study drug.

The company's risk of bias assessment of QuANTUM-First is reported in Appendix D.1.4 of the CS. The EAG broadly agrees with the company that QuANTUM-First is at low risk of bias overall. Major protocol violations took place in 277 (51.4%) patients overall and were similar between arms (141 [52.6%] patients in the quizartinib arm and 136 [50.2%]). The most common deviations were associated with administration of the incorrect dose as per protocol in any phase (17.5% vs 13.3%) and late reporting of serious adverse events (SAEs) (13.1% vs 15.1%). Overall, 42 (15.8%) patients in the quizartinib arm and 87 (32.5%) patients in the placebo arm received a non-protocol-specified AML therapies; the most common treatment was cytarabine, used 29 [10.9%] patients in the quizartinib arm and 57 [21.3%] patients in the placebo arm). A total of 15.6% and 13.6% of patients received non-protocol specified HSCT in the quizartinib and placebo arms respectively.

3.2.1.1 EAG Comments

The EAG considers the trial design broadly appropriate to evaluate the relative effectiveness and safety of quizartinib against placebo across all treatment phases. However, the trial was not designed

to evaluate the efficacy and safety of each treatment phase separately, the clinical benefits and harms of quizartinib during the induction, consolidation, and maintenance phases, and among patients with and without HSCT, cannot be completely isolated by phase. Consequently, the relative efficacy and safety of quizartinib and placebo in the consolidation, maintenance and long-term follow-up phases is uncertain and may be confounded by the efficacy, safety and cumulative toxicity of treatments received in prior phases.

The rate of protocol deviations, including non-protocol specified therapies, was high in both arms; it is unclear whether and to what extent the differences in the use of non-protocol specified therapies between quizartinib and placebo may have affected the efficacy and safety results.

The company confirmed that MRD (minimal or measurable residual disease) assessment was not used to determine whether to proceed with HSCT (response to clarification question A8). Whilst this was representative of clinical practice at the time of the QuANTUM-First trial, this may limit the generalisability of the trial procedures to current practice (see Issue 5 in Section 3.4.1.1).

The lack of head-to-head comparison against relevant comparators midostaurin (and sorafenib in the post-HSCT maintenance setting) limits the extent to which QuANTUM-First can address the company's decision problem and requires ITCs to be performed (Section 3.5).

3.2.2 Population

Adults (defined as individuals ≥ 18 years old or the minimum legal adult age, whichever was greater, and ≤ 75 years old) with either ND, morphologically documented primary AML or AML secondary to MDS or an MPN based on the WHO classification criteria (at screening) who had an *FLT3-ITD+* mutation in bone marrow were eligible for inclusion in the trial. The QuANTUM-First trial excluded patients with uncontrolled or significant cardiovascular disease, due to the increased risk of developing QTc interval prolongation and cardiac arrhythmia events associated with quizartinib. Further eligibility criteria of the QuANTUM-First trial are described in CS, Table 5.

To be eligible for the consolidation phase, patients needed to have achieved CR or CRi (based on local laboratory results) at the end of the induction phase and could begin consolidation within 60 days of day 1 of the last induction cycle. To be eligible for the maintenance phase, patients who had undergone HSCT must not have active acute or ≥ grade 3 graft vs. host disease (GVHD) nor should they have initiated therapy for active GVHD within 21 days. Patients were also required to have an absolute neutrophil count (ANC) > 500/mm^3, a platelet count > 50,000/mm^3 (without platelet transfusion support) within 24 hours prior to the first day of cycle 1 of maintenance therapy and confirmed < 5% of blasts based on the most recent bone marrow aspirate (based on local laboratory results) within 28 days prior to the first day of cycle 1 of maintenance therapy. Patients were required

to begin maintenance treatment within 60 days of day 1 of the last consolidation cycle, or within 180 days after HSCT.

Baseline characteristics for patients included in QuANTUM-First are reported in Appendix Table 43.

3.2.2.1 EAG comments

Clinical advice to the EAG indicated that the QuANTUM-First trial population is largely representative of the NHS population and representative of both those who would be eligible for intensive chemotherapy and quizartinib on the NHS.

The EAG considers there to be no evidence of imbalances between the two treatment arms.

3.2.3 Trial outcomes

Primary, secondary, and exploratory efficacy outcomes of the QuANTUM First trial were as follows:

- **Primary efficacy outcome:** overall survival (OS)
- **Secondary efficacy outcomes:** event-free survival (EFS, FDA definition [primary analysis] and protocol definition [sensitivity analysis]; CS Section 2.6.2) and complete remission (CR) and composite complete remission (CRc) rates
- **Exploratory efficacy outcomes:** relapse-free survival (RFS), duration of CR, transplantation rate, and QoL.
- **Post-hoc efficacy analyses:** CR and CRc rates in patients with *FLT3-ITD* MRD negativity; cumulative incidence of relapse (CIR) from randomisation in patients with CR in the induction phase.

The primary endpoint in the initial protocol was EFS. Following a protocol amendment (April 2020) which took place after the end of participant recruitment (August 2019), the primary endpoint was changed from EFS to dual primary endpoints of EFS and OS, and subsequently, to a secondary endpoint (following feedback from the FDA and AML guidance)[26], and OS was made the sole primary endpoint. The definition of EFS was changed in a subsequent protocol amendment, which the company stated was to align with AML guidance. Further details are reported in the CSR, Table 6.7.[27]

Outcome definitions, including response criteria, are described in CS, Table 6. OS, CR and CIR are incorporated into the company model.

3.2.3.1 Subgroup Analyses

For OS and EFS, the company included pre-planned subgroup analyses on demographic characteristics (age, sex, race, and geographical region), and baseline characteristics (ECOG PS, WBC count at the time of diagnosis, choice of anthracycline used during the induction phase, AML

cytogenic risk score, *FLT3*-ITD variant allele frequency (VAF) at randomisation, and *NPM1* mutational status (CS, Document B, Table 5).

For safety outcomes, the company conducted pre-planned subgroup analyses of treatment-emergent adverse events (TEAEs) on patient age, sex, race, and the anthracycline used during the induction phase. Another subgroup analysis was conducted to evaluate the effects of age, sex, use of strong CYP3A4 inhibitors and the use of medications to prolong the QT on electrocardiogram (ECG) results.

3.2.3.2 EAG Comments

The EAG considers that the outcomes evaluated by the company are appropriate and evidence has been provided for all outcomes outlined in the NICE scope. However, the EAG has concerns regarding the selection and definition of certain key outcomes.

EFS was originally the primary endpoint of this trial in the initial versions of the protocol. The protocol was later amended, first to make OS a joint primary outcome, and subsequently to designate OS as the sole primary outcome, with event-free survival (EFS) included as a secondary outcome. It appears that the amendments took place after the completion of participant recruitment but before the database lock. The CSR stated that the change of EFS from primary to secondary endpoint was based on FDA feedback and AML guidance from the FDA.[26] It is, however, unclear which specific aspects of the guidance informed these major protocol deviations.

Clinical advice to the EAG indicated most patients will achieve CR within the first treatment cycle (42 days) and whilst a small proportion will require two courses to achieve CR, a cut-off of 42 days to achieve CR is reflective of current clinical practice. Therefore, the EAG considers that the FDA-recommended definition of ITF (induction treatment failure) for their primary EFS analysis, which provides a 42-day window for patients to achieve CR, is more reflective of NHS clinical practice than the later cut-off of 56 days used by the company.

Although relevant to the economic model (see Section 4.2.6), the analyses of CR and CRc in MRD negative patients, and CIR should be treated with caution as they were not pre-specified and as they were conducted in subgroups of the ITT population who achieved remission so are not balanced by randomisation and thus may be at risk of confounding bias.

3.2.4 Results

A summary of the results for the clinical effectiveness outcomes is provided in Table 5. Complete results are reported in Section B.2.6 of the CS. Results presented in the CS correspond to a data cut-off date of 13 August 2021 and a median follow-up time in the ITT population of 39.2 months. All efficacy analyses were performed on the intention-to-treat (ITT) population (CS, Table 7).

Table 5 Summary of QuANTUM-First effectiveness results

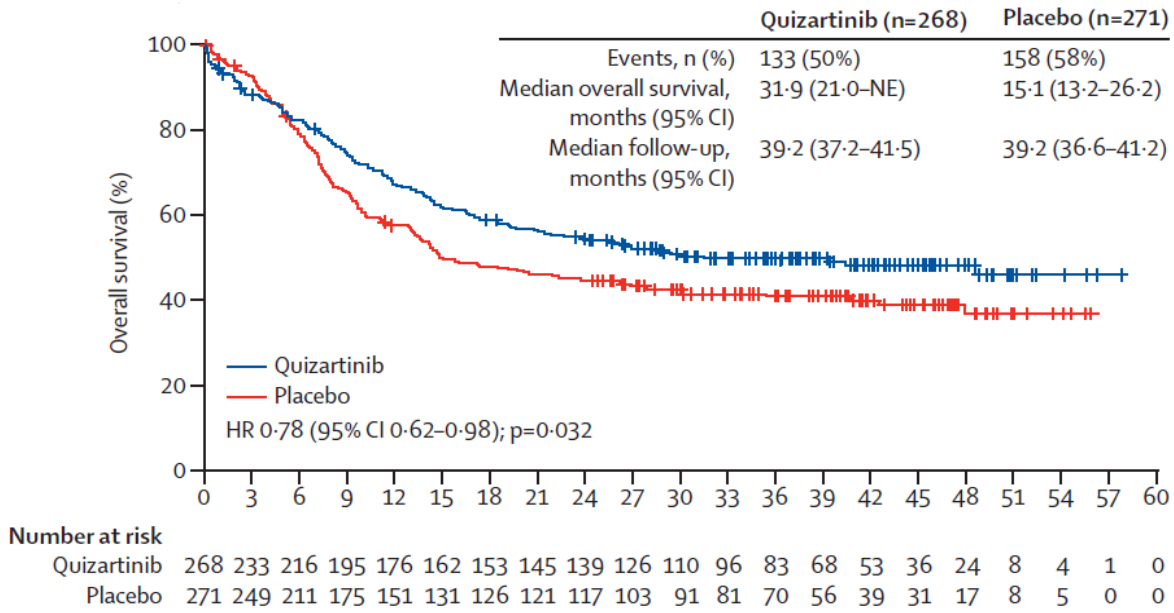
	Quizartinib (N=268)	**Placebo (N=271)**
Overall Survival		
Events (deaths), n (%)	133 (49.6)	158 (58.3)
HR (95% CI) [a,b]	0.776 (0.615, 0.979)	
Median OS (95% CI)[c], months	31.9 (21.0, NE)	15.1 (13.2, 26.2)
Event-free Survival (IRC assessment, FDA definition of ITF)		
Events, n (%)	198 (73.9)	213 (78.6)
HR (95% CI) [a,b]	0.92 (0.75, 1.11)	
Median EFS (95% CI)[c], months	0.03 (0.03, 0.95)	0.71 (0.03, 3.42)
CR		
Rate (%) (95% CI[d])	54.9 (48.7, 60.9)	55.4 (49.2, 61.4)
Duration of CR		
Median duration of CR (95% CI), months	38.6 (21.9, NE)	12.4 (8.8, 22.7)
HR (95% CI)	0.621 (0.451, 0.857)	
CRc		
Rate (%) (95% CI[d])	71.6 (65.8, 77.0)	64.9 (58.9, 70.6)
Cri		
Rate (%) (95% CI[d])	16.8 (12.5, 21.8)	9.6 (6.4, 13.7)
Relapse-free Survival		
Events, n (% of patients with CRc)	95 (49.5)	102 (58.0)
HR (95% CI)[e]	0.733 (0.554, 0.969)	
Median RFS (95% CI)[c], months	28.5 (18.5, NE)	12.6 (9.7, 23.7)
Cumulative Incidence of Relapse (CIR)		
Events, n (% of patients with CR)	44 (30)	63 (42)
HR (95% CI)	[redacted]	
Transplantation rate		
Protocol-specified HSCT[f] : Rate (%) (95% CI)[g]	38.1 (32.2, 44.2)	33.6 (28.0, 39.5)
Protocol-specified HSCT[f] and non-protocol-specified HSCT[h] : Rate (%) (95% CI)	53.7 (47.6, 59.8)	47.2 (41.2, 53.4)
Quality of Life		
EQ-5D-5L Index score (UK value set) MMRM for CfB	-0.0183 (95% CI: -0.0463, -0.0098)[i] p = 0.20	

Abbreviations: AML, acute myeloid leukaemia; CfB, change from baseline; CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; *FLT3*, FMS-like kinase 3; EFS, event-free survival; HR, hazard ratio; HSCT, allogeneic hematopoietic stem cell transplantation; IRC, independent review committee; *ITD*, internal tandem duplication; ITF, induction treatment failure; KM, Kaplan Meier; MMRM, mixed-effects model for repeated measures; MRD, minimal or measurable residual disease; NR not reported; OS, overall survival; RFS, relapse-free survival, WBC, white blood cell.
a Stratified Cox regression analysis.
b. Stratification factors include region (North America, Europe, Asia/other regions), age (<60, ≥ 60 years old), and WBC count at the time of diagnosis of AML (<40×10^9/L, ≥40 ×10^9/L).
c. Median is from the KM analysis, CI is computed using the Brookmeyer-Crowley method.
d. Estimated using the KM method.
e. Unstratified Cox regression analysis.
f. Patients with protocol-specified HSCT are patients who underwent HSCT following protocol treatment with no intervening AML therapy (excluding conditioning regiments).
g. Based on the Clopper-Pearson method.
h. Any HSCT performed for other reasons, e.g. molecular relapse, will be considered non-protocol-specified AML therapy, and the subject will be discontinued from quizartinib or placebo but will continue to be followed for outcome data.
i. Least square mean difference, quizartinib vs. placebo.

3.2.4.1 Overall Survival

As of the August 2021 data cut-off, 133 (49.6%) patients in the quizartinib and 158 (58.3%) patients in the placebo arm had died. Median OS was longer in the quizartinib arm compared to placebo, resulting in a 22.4% reduction in the risk of death (Hazard Ratio (HR): 0.78; 95% CI: 0.62 to 0.98, p =0.03). The Kaplan-Meier (KM) plot for OS is reproduced in Figure 3.

Figure 3 Kaplan-Meier plot of overall survival (ITT analysis set)



Reproduced from CS Document B, Figure 5. Source: Erba et al. 2023[28]
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable.
Notes: Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test. Data cut-off date: 13 Aug 2021

Supplementary/Sensitivity Analyses

Results for supplementary/sensitivity analyses for OS are presented in CS, Document B, pp. 62-64.

A sensitivity analysis of OS that censored patients who received HSCT at any time during the study showed that the median OS was longer in the quizartinib arm (20.8 months; 95% CI: 14.3 to 28.9) compared to the placebo arm (12.9 months; 95% CI: 9.2 to 14.7) and the risk of death was numerically reduced in the quizartinib arm compared to the placebo arm (HR: 0.75, 95% CI: 0.56 to 1.01, p = 0.055), but the difference between treatment arms was not statistically significant.

To account for a potential 'plateau effect' in OS, due to a similar effect (i.e. flattening of KM curves around 30 months) observed in the RATIFY trial, the company used the restricted mean survival time (RMST) method to analyse OS. The RMST in the quizartinib treatment arm was [redacted] months, and [redacted] months in the placebo treatment arm. Compared with placebo, the estimated RMST survival time for patients who received quizartinib was prolonged by [redacted]

EAG Comments

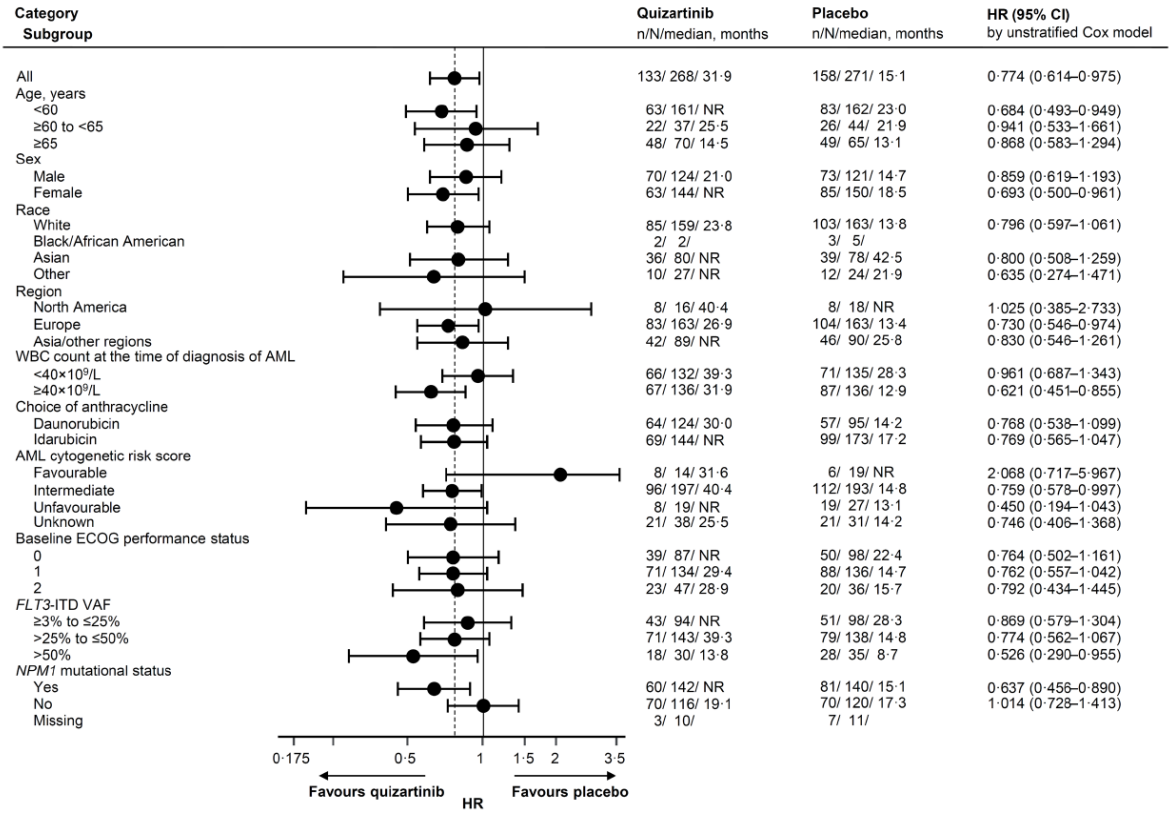
Upon visual inspection of the KM plot, the EAG notes a plateau in the survival curves around 30 months, along with a higher incidence of early deaths in the quizartinib treatment arm compared to the placebo arm. For this reason, the EAG considers that a comparison of median OS values between quizartinib and placebo is of limited value, as the median values are unlikely to capture the true treatment effect. The EAG considers that the comparison of RMST survival time to be a more appropriate measure of the relative difference in survival time between quizartinib and placebo.

The intersection of the KM curves at approximately 6 months, suggests that the proportional hazards (PH) assumption is not met. Company assessments demonstrate that the PH assumption is violated for both OS (primary analysis) and OS censored at the time of HSCT (response to clarification questions A6a and A6c) The HRs estimated for both these outcomes should therefore be interpreted carefully as this will not be reflective of relative efficacy at all time points.

Subgroup analyses

Subgroup analysis results for OS are presented in the forest plot in Figure 4. Further results from subgroup analyses conducted on OS and EFS are presented in in Appendix E of the CS.

Figure 4 Forest plot for subgroup analyses for OS (ITT Population)



Source: Erba et al. 2023 [29]

Abbreviations: AML: acute myeloid leukaemia; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; *FLT3-ITD*: FMS-like tyrosine kinase 3 internal tandem duplication; ITT: intention to treat; n: number of events; N: number of patients; NE: not estimable; *NPM1*: nucleophosmin 1; OS: overall survival; WBC: white blood cell.

Notes: Hazard ratio was obtained from the unstratified Cox proportional hazard model. The dotted line indicates the hazard ratio for the overall OS analysis. Median OS is from the Kaplan-Meier analysis.

Subgroup analyses in the maintenance setting with and without prior HSCT

Following a request for clarification from the EAG (question A3), the company provided additional evidence from an exploratory, post-hoc subgroup analysis originally requested by the FDA to inform OS outcomes for individuals undergoing maintenance therapy in QuANTUM-First, reported in the prescribing information for quizartinib.[1] The subgroup analysis included only individuals who entered the maintenance phase of the study (N=208, where 116 in quizartinib and 92 in placebo arm). Results are presented in Table 6,

Figure 5, and Figure 6.

OS was analysed from randomization separately for the subgroups with and without HSCT, and the HR with 95% CI was estimated using unstratified Cox regression. The median OS (95% CI) was not reached in either treatment arm in the group of subjects with HSCT prior to maintenance. The analysis for the subgroup with HSCT showed a numerical difference favouring placebo over quizartinib (HR 1.62 [95% CI 0.62, 4.22]), although the confidence interval was wide notably due to the small number of events and not statistically significant. The subgroup analysis of patients without prior HSCT showed a statistically significant difference favouring quizartinib compared with placebo (HR 0.40 95% CI 0.19 to 0.84).

KM curves for patients with HSCT prior to maintenance is presented in

Figure 5, which shows little difference in OS events between quizartinib and placebo until approximately 27-30 months, at which point the quizartinib curve slightly departs from the plateau observed in the placebo curve, along with significant censoring in both arms.

Figure 6 presents the results for the subgroup without HSCT at around 9 months, prior to maintenance, and shows a clear separation of the two KM curves between the two treatments arms, and significantly more favourable OS results for quizartinib.

Table 6 OS outcomes in the maintenance setting with/without HSCT prior to maintenance

Statistics	With HSCT Prior to Maintenance[a]		Without HSCT Prior to Maintenance[b]	
	Quizartinib (N = 70)	Placebo (N = 49)	Quizartinib (N = 46)	Placebo (N = 43)
Subjects (%) with events (deaths)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (months)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	1.62 (0.62 to 4.22)		0.40 (0.19 to 0.84)	

Source: Company clarification response, Question A3, Table 1
Abbreviations: CI, confidence interval; HSCT, allogeneic hematopoietic stem cell transplantation; ITT, intent-to-treat; NE, not estimable; OS, overall survival
a Includes subjects who received consolidation chemotherapy + HSCT and those who received HSCT alone during the Consolidation Phase
b Includes subjects who received only consolidation chemotherapy during the Consolidation Phase
c Median OS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.
Note: OS is the time from Randomization until the date of death from any cause. Denominator for percentages is the number of subjects in the ITT Analysis Set in each HSCT status subgroup.

Figure 5 KM Plot of OS for Subjects Who Entered the Maintenance Phase With HSCT Prior to Maintenance (ITT Analysis Set)

Source: Company clarification response, Question A3, Figure 1
Abbreviations: HSCT, hematopoietic stem cell transplantation; ITT, Intent-to-treat.

Figure 6 KM Plot of OS for Subjects Who Entered the Maintenance Phase Without HSCT Prior to Maintenance (ITT Analysis Set)

Source: Company clarification response, Question A3, Figure 2
Abbreviations: HSCT, hematopoietic stem cell transplantation; ITT, Intent-to-treat.

EAG Comments

OS subgroup analyses showed potential evidence of heterogeneity by age, sex, WBC count, and *NPM1* mutation status. Quizartinib appeared to be beneficial for patients aged under 60 years, whereas there was no evidence of OS benefits from quizartinib in patients aged either 60 to 65 years or over 65 years. There was also no evidence of OS benefit in male patients. Quizartinib also appeared to be beneficial compared to placebo in patients who had a WBC count of $\geq 40 \times 10^9$/L at the time of diagnosis of AML, and >50% *FLT3-ITD* VAF. Subgroup analysis also suggests that patients from the favourable cytogenetic risk group may have better survival in the placebo treatment arm, although the 95% CI intercepts the line of no treatment effect. The results for EFS were consistent across subgroups with the primary analysis and 95% CIs for all HRs intersected the line of no treatment effect. As in the subgroup analysis for OS, it appeared that patients with a favourable cytogenic scores responded (numerically) better to placebo than quizartinib, and there was no evidence of any benefit for quizartinib over placebo for patients aged over 60 and over 65 years. The EAG sought clinical advice and clarification from the company regarding these results, although no conclusive explanation could be provided. The EAG notes that the QuANTUM-First trial was not powered to detect differences in OS and EFS within subgroups, and many subgroup results are associated with uncertainty due to small sample sizes and wide 95% CIs around the HRs. Therefore, all subgroup analysis results should be interpreted with caution.

The subgroup analyses of OS outcomes in the maintenance setting show distinctly different patterns between participants with and without prior HSCT. Whilst these analyses suggest that patients with no prior HSCT have clinically and statistically significantly better OS outcomes with quizartinib compared with placebo, the analyses of patients with prior HSCT show no evidence that quizartinib has superior OS outcomes to placebo in this subgroup. Although the HR estimate may indicate that quizartinib is associated with worse survival outcomes in this population, the EAG agrees with the company that the wide confidence interval observed in the post-HSCT subgroup analysis means that no definitive conclusions can be drawn. The EAG also recognise that these analyses are limited by significant censoring after approximately 24 months. Whilst these analyses account for the effect of HSCT on survival, the comparisons between quizartinib and placebo are not conducted from the point of initiating maintenance therapy and may be biased by unadjusted between-group differences and the confounding impact of prior induction/consolidation phases.

3.2.4.2 Secondary Outcomes

Event-free Survival

As of the August 2021 data cut-off, 198 (73.9%) of the patients in the quizartinib arm and 213 (78.6%) of the patients in the placebo arm had experienced an EFS event, assessed by an Independent Review Committee (IRC). The median EFS, estimated by the KM method, was short in both the

quizartinib (0.03 months; 95% CI: 0.03 to 0.95) and placebo (0.71; 95% CI: 0.03 to 3.42) arms. The difference between the two treatment arms was not statistically significant (HR: 0.92; 95% CI: 0.75 to 1.11, p = 0.24). The company attributed the short median EFS values in their primary analysis as it included the FDA recommended definition of EFS, which includes failure to achieve CR within 42 days from the start of the last induction chemotherapy The company outlined that extending the period in which CRc is assessed to align with current AML guidelines allows a more meaningful assessment of EFS as it permits patients to recover from the myelosuppressive effects of quizartinib (CS, pp. 64-65).

When using the protocol definition of EFS (i.e. not achieving CRc by the end of the induction phase up to day 56), the difference between the two treatment arms was statistically significant (HR: 0.73; 95% CI: 0.59 to 0.90, p=0.003). Also, when using the definition of EFS recommended by the current European Society for Medical Oncology (EMSO), ELN and an AML working group (i.e. not achieving CR by the end of the induction phase up to day 56) gives a statistically significant difference between the two treatment arms (HR: 0.82, 95% CI: 0.67 to 0.999, p =0.032) (CS, Document B, Table 15).

CR and Composite complete remission (CRc) rates

At the end of the induction phase, CR was similar between the quizartinib and placebo treatment arms (54.9% and 55.4% respectively). The CRc rate was numerically higher in the quizartinib treatment arm than the placebo arm (71.6% versus 64.9% respectively) due to a higher CRi rate on quizartinib treatment compared to placebo (16.8% versus 9.8%). The company did not test for the statistical significance of these differences, due to the hierarchical statistical testing approach for secondary outcomes as specified in the trial protocol. The company explained that the higher rate of incomplete haematological recovery could be due to the initial myelosuppressive effects of quizartinib in the induction phase and how sensitive recovery is to the window of time used for response assessment (CS, p69).

Post-hoc analysis: CR and CRc rates in patients with FLT3-ITD MRD negativity

This post-hoc analysis was conducted in 308 (84%) of the 368 patients who achieved CRc after induction. The proportion of patients in CRc with *FLT3*-ITD MRD negativity ($<1 \times 10^{-4}$) was similar in both treatment arms: 24.6% in the quizartinib and 21.4% in the placebo arms. The proportion of patients in CRc with undetectable *FLT3*-ITD MRD ($<1 \times 10^{-5}$) was greater in the quizartinib arm (13.8%) compared to placebo (7.4%) (p=0.017). Similarly, among patients who achieved CR, 20.1% were FLT3-ITD MRD negative ($<1 \times 10^{-4}$) in the quizartinib arm compared with 18.8% in the placebo arm. In the quizartinib arm,10.8% of CR patients had undetected *FLT3*-ITD MRD compared with 7.0% in the placebo arm (CS, Document B, p78).

EAG Comments

As for OS, the PH assumption appears to be violated for EFS analyses with implications for the interpretation of estimated HR (response to clarification question A6d).

The EAG highlights the sensitivity of point estimates to the definition of EFS and notes the lack of a statistically significant treatment effect when EFS is defined according to the original ITF definition. The EAG, however, accepts that post-hoc definitions are likely more reflective of current guideline.

3.2.4.3 Exploratory Outcomes

Relapse-free survival

The median RFS in patients who achieved CRc during the induction phase was longer in the quizartinib arm (28.5 months) compared to the placebo arm (12.6 months). The HR comparing RFS in the quizartinib arm to placebo was 0.733 (95% CI: 0.554 to 0.969). The company conducted an additional analysis of RFS in patients who had achieved CR during induction. Median RFS in patients who had achieved CR during induction was longer in the quizartinib arm (39.3 months; 95% CI: 22.6-NE) compared to the placebo arm (13.6 months; 95% CI: 9.7 to 23.7) with a HR of 0.61 (95% CI: 0.44 to 0.85; CS, Document B, pp.69-72)

Duration of CR

Median duration of CR was longer in the quizartinib treatment arm (38.6 months) compared to placebo (12.4 months). Compared to placebo, the probability of maintaining CR was higher for quizartinib at all timepoints up to 3 years (CS, Document B. Table 19).

Transplantation rate

A similar number of patients in both treatment arms underwent both protocol-specified (38.1% in quizartinib and 33.6% in the placebo arm) and non-protocol-specified (15.6% in the quizartinib and 13.6% in the placebo arm) HSCT (CS, Document B, Table 20).

Cumulative incidence of relapse (CIR)

CIR rates were lower in the quizartinib arm than the placebo arm ([redacted]), which the company interpret as suggesting that quizartinib may prevent or delay relapses (CS, Document B, pp.78-79).

Quality of Life (QoL)

The PRO analysis dataset consisted of 509 patients: 254 and 255 patients in the quizartinib and placebo treatment arms, respectively. The UK value set for the index score were calculated using the mapping function recommended by NICE.[30, 31]

498 patients (98%) completed an EQ-5D-5L index score at PRO baseline. PRO baseline scores were similar in both treatment arms: the mean EQ-5D-5L score ± standard deviation was [redacted] in the quizartinib arm and [redacted] in the placebo arm. By visit, the compliance rate ranged from [redacted] to [redacted] for the quizartinib arm, and [redacted] to [redacted] for the placebo arm.

To analyse changes in EQ-5D-5 scores over time, a mixed-effects model for repeated measures was conducted to adjust for the baseline score, treatment, time, and the treatment-time interaction. This analysis showed an improvement in EQ-5D-5L scores compared to baseline in both treatment arms (CS, Document B, Figure 13). While the improvement over time for both treatment arms was on average greater than the MCID, no clinically meaningful difference was observed between the two treatment arms (least squares mean difference = [redacted]).

EAG Comments

Analyses for RFS, duration of CR, transplantation rate, CIR and QoL were not pre-specified and should be interpreted as exploratory. The PH assumption was not met for analyses of RFS and duration of CR, as evidenced by additional analyses conducted by the company in response clarification question A6. All QoL results should be interpreted with caution as QuANTUM-First was not designed to compare the differences in treatment effect of quizartinib compared to placebo on PROs. P-values for exploratory outcomes were not reported and any nominal differences between quizartinib and placebo should be interpreted with caution.

3.2.4.4 Safety

Results for adverse events (AEs) are presented in Section B.2.10 of the CS. A summary of adverse events for each treatment phase and the overall trial is presented in Appendix Table 46.

Treatment-emergent adverse events (TEAEs)

Almost all patients (99.6% of patients in the quizartinib and 98.9% of patients in the placebo arm) in QuANTUM-First experienced at least one TEAE overall. A summary of the most-commonly observed TEAEs is given in CS, Table 35. The most common TEAEs were consistent in both treatment arms: febrile neutropenia (n = 117, 44.2% in quizartinib and n=113, 42.2% in placebo), pyrexia (n = 112, 42.3% in quizartinib and n=109, 40.7% in placebo), diarrhoea (n = 98, 37% in quizartinib and n=94, 35.1% in placebo), and hypokalaemia (n = 93, 35.1% in quizartinib and n=96, 35.8% in placebo). A similar percentage of patients in both treatment arms experienced at least one severe (grade ≥ 3) TEAEs (92.1% in the quizartinib arm and 89.6% in the placebo arm).

Study-drug related TEAEs

A higher percentage of patients in the quizartinib treatment arm (60.4%) experienced TEAEs that were attributed to the study drug by trial investigators compared to the placebo treatment arm (36.2%), overall. The difference between the two treatment arms occurred mostly during the

maintenance phase (73.3% of patients in the quizartinib arm compared to 37.0% in placebo), although a higher percentage of patients in the quizartinib arm (38.5% compared to 28.7% in placebo) also experienced study-drug related TEAEs during the induction phase (CS, Document B, Table 40). The most commonly observed study-drug related TEAEs were cytopenias (neutropenia, thrombocytopenia, decrease in neutrophil count, febrile neutropenia, and anaemia), ECG QT prolonged, gastrointestinal disorders (nausea and diarrhoea), increased alanine aminotransferase, and pyrexia (CS, Document B, Table 36).

Deaths

More early deaths were observed in the quizartinib arm; [redacted] patients in the quizartinib arm and [redacted] patients in the placebo arm died within 30 days of drug administration; at 60 days, [redacted] patients in the quizartinib arm, and [redacted] in the placebo arm had died. These deaths were mostly due to infections (CS, Document B, Table 38).

Serious adverse event (SAE)

A summary of SAEs is presented in CS, Document B, Table 37. SAEs were more commonly observed in the quizartinib treatment arm (54% of patients) compared to placebo (46% of patients). The most commonly observed SAEs were infections (pneumonia, septic shock, and sepsis), blood disorders (febrile neutropenia, and thrombocytopenia), and pyrexia; 28.7% of the 143 SAEs in the quizartinib arm and 23.6% of the 123 SAEs in the placebo arm were study-drug related according to the study investigator. 30 patients (11.3%) in the quizartinib arm and 26 patients (9.7%) in the placebo arm experienced a fatal SAE. In both treatment arms, 4 of these deaths were attributed to the study drug according to the study investigator (CS, Document B, Table 38).

TEAEs associated with dose discontinuation and modification

A higher percentage of patients in the quizartinib arm experienced TEAEs that resulted in study drug discontinuation, dose-reduction, or interruption. Most of these events occurred during the maintenance phase of the trial

Adverse events of special interest (AESI)

The company considered QTcF prolongation and combined elevation of aminotransferases and bilirubin AESIs. 6 (2.3%) patients in the quizartinib arm and 2 (0.7%) patients in the placebo arm experienced a grade 3-4 QTcF prolongation based on central ECG readings. Two patients in the quizartinib arm experienced cardiac arrest with ventricular fibrillation during the induction phase. More details on combined elevation of aminotransferase and bilirubin AESIs are included in CS, Appendix F. A higher incidence of QTcF prolongation (>450 ms) was observed overall in the quizartinib arm compared with the placebo arm across most subgroups, except for the male and aged ≥65 years and subgroups. Further details are reported in the CSR, Section 10.9.2.

EAG Comments

Numerically higher rates of AEs, treatment-related AEs, SAEs, early deaths and discontinuations/dose adjustments of study drug due to AEs were observed in the quizartinib arm compared to placebo. Of note, rates of neutropenia and QT prolongation that were considered to be treatment-related by the investigator were numerically more frequent in the quizartinib arm. Although most QT prolongation were non-serious and resolved, cardiac deaths were reported in the quizartinib arm, and the EAG agrees with the EMA that, based on the available trial evidence, the "impact of cardiac risks may be underestimated".[32] The tolerability of quizartinib was notably more limited in the maintenance phase. Most treatment-related AEs, discontinuations/dose adjustments of study drug due to AEs were observed during the maintenance phase, and most patients did not complete the full maintenance course of 36 cycles, although there was no evidence of increased risk for death due to AEs.

3.3 Critique of trials identified and considered for the indirect comparisons

This section discusses trial evidence for comparators that EAG considers relevant to inform the decision problem. Section 3.3.1 discusses trials of midostaurin across the induction, consolidation and maintenance phases. Section 3.3.2 examines trial evidence for sorafenib in the post-HSCT maintenance setting.

3.3.1 Trials of midostaurin across the induction, consolidation and maintenance phases

The company's systematic review included one RCT and two single-arm trials of midostaurin. [33-35] Of those, only the RATIFY RCT was included in the ITC. The characteristics of all studies included in the company's SLR are reported in CS, Appendix D, Table 17. Whilst the EAG agrees with the company that the exclusion of Sierra *et al*. 2020,[35] which was reported as a conference abstract only, was justified, the EAG considered that trial AMSLG 16-10 may provide relevant supportive evidence and address evidence gaps from RATIFY. The EAG believes that the inclusion of RATIFY in the ITC is appropriate but noted that the trial was limited in its ability to inform the decision problem as it excludes participants over 60 years, lacks CRi and CRc outcome data and data on several relevant treatment effect modifiers (see Sections 3.4.1 and 3.5.1). This section provides a summary and critique of the RATIFY and AMSLG 16-10 trials.

3.3.1.1 RATIFY

The methodology of the RATIFY trial is summarised in CS, Appendix D, Section D.1.2.3.1

Trial design

RATIFY was an international phase 3, placebo-controlled double-blind, randomised study that examined the efficacy and safety of midostaurin + standard chemotherapy compared with placebo + standard chemotherapy in subjects with newly diagnosed *FLT3*+ AML. A total of 717 adult patients aged between 18 and 59 years from 17 countries were randomised 1-1 to standard chemotherapy plus either midostaurin or placebo. Randomisation was stratified according to subtype of FLT3 mutation: TKD, ITD_{high} or ITD_{low}. The trial was conducted between April 2008 and July 2016.

RATIFY comprised three consecutive treatment phases: induction, consolidation and maintenance. Details of the treatment phases and chemotherapy doses are included in CS, Appendix D, Table 6. Clinical advice to the EAG confirmed that these broadly reflected NHS practice.

The primary outcome for the study was OS. An event was defined as a death from any cause and measured as the time to the event from randomisation plus one day. Definitions of primary and secondary outcomes in RATIFY are listed in CS, Document B, Table 22. Similarly to QuANTUM-First, CR had to occur by day 60, but also included CR during a second induction cycle, effectively

adding up to 120 days. An EFS event was defined as a failure to obtain a CR within 60 days of initiation of protocol therapy, or relapse from CR, or death from any cause, whichever occurred first.

Subgroup analyses were conducted on OS and EFS according to *FLT3* mutation (including the *FLT3-ITD*+ mutation). In the initial RATIFY trial publication, [33] the results for the *FLT3-ITD* population were separated into two subtypes, *FLT3-ITD* with either a high ratio (>0.7) or low ratio (0.05 to 0.7) of mutant to wild-type alleles. In a subsequent publication, [36] a retrospective post-hoc analysis that used data from 452 patients from the RATIFY trial to evaluate the molecular landscape of *FLT3-ITD* and assess the prognostic impact of the *ITD* mutation on OS and cumulative incident relapse (CIR). Results for both publications are reported in CS, Appendix D Section D.1.2.3.7.

Trial population

The RATIFY trial included 717 patients with diagnosed *FLT3*+-mutation-positive (*FLT3-ITD* or *FLT3-TKD*) AML between 18 and 59 years old. Patients were excluded if they had therapy-related AML, raised total bilirubin or had symptomatic congestive heart failure, as were patients who had received prior chemotherapy for myelodysplasia.

Results

A total of 452 *FLT3-ITD*+ patients were included; their characteristics are summarised in CS Document B, Table 23. The median age in this subgroup was 47 years (range 18-60). Whilst most baseline characteristics were balanced between the midostaurin and placebo arms in this subgroup, there were statistically significant differences for some variables, including: abnormal karyotype (37.8% in the midostaurin arm, vs. 19.9% in the placebo arm); *NPM1* mutation (50.0% vs. 64.3%).

A summary of the results for the clinical effectiveness outcomes is reported in CS, Appendix D, Section D.1.2.3. In the *FLT3-ITD*+ population, patients treated with midostaurin had numerically better OS (HR = 0.79; 95% CI 0.59 to 1.06, p-value = 0.120) and CIR (HR = 0.80; 95% CI 0.56 to 1.15, p-value = 0.222) compared with placebo; however, these results were not statistically significant.

EAG Comments

The EAG generally agrees with the company's risk of bias assessment of the RATIFY trial. Although insufficient information was reported to assess the risk of attrition bias, the EAG found the trial to be at low risk of bias overall (see Appendix Table 44 for further details).

The RATIFY trial included patients with *FLT3-ITD* and *FLT3-TKD* mutations. Although randomisation was stratified by *FLT3* mutation and effectiveness results were reported for each subgroup separately, some statistically significant imbalances were found between the midostaurin and placebo arms in the *FLT3-ITD*+ subgroup. Although these imbalances may have occurred by

chance alone, the risk that they may have introduced bias to the efficacy and safety results cannot be excluded. Whilst the higher rate of abnormal karyotype and lower rate of *NPM1* mutation in the midostaurin arm may favour the prognosis of patients receiving placebo over midostaurin, the direction and magnitude of any possible impact of these imbalances on the treatment effect is difficult to ascertain.

As per Section 3.2.3.2, clinical advice to the EAG indicated most patients will be expected to achieve CR within the first treatment cycle (42 days), whilst a small proportion will require two courses to achieve CR, a cut-off of 42 days to achieve CR is more reflective of current clinical practice than the 60 days cut-off used in RATIFY. Similarly to QuANTUM-First, this limits the applicability of the CR results and EFS results, which use the CR cut-off of 60 days, to clinical practice.

Due to the age restrictions and median age of the RATIFY trial, the applicability of the findings to current UK practice is limited. Clinical advice to the EAG has indicated there has been incremental improvement in the treatment and management of AML over time.[37] This includes better supportive care, improved management of chemotherapy toxicity and increased availability of transplant donors have improved treatment outcomes for people with AML. In addition, the criteria for HSCT eligibility have evolved, as the decision-making process now incorporates MRD assessment.

Current UK practice allows for patients over 60 to be treated with midostaurin. As this age group was excluded from the trial, the generalisability of the results to older patients is uncertain. The EAG highlights this was a major concern in TA523 and the committee concluded that the average age of people likely to have midostaurin is higher than the average age of people in the trial.

The results for the subgroup of *FLT3-ITD*+ patients did not show a statistically significant difference in OS and CIR. These results should be interpreted with caution, as these are based on post-hoc subgroup analyses that may not have been sufficiently powered for these outcomes.

3.3.1.2 AMSLG 16-10

The AMLSG 16-10 trial is a single-arm, open-label trial that evaluated midostaurin with intensive (standard) chemotherapy including induction and consolidation followed by HSCT and a 1-year midostaurin maintenance therapy in *FLT3-ITD*+ AML patients. The trial included 440 patients with newly diagnosed *FLT3-ITD*+ AML with an age ranging from 18 to 70 years. The baseline characteristics are summarised in Table 7.

Table 7 Baseline characteristics of AMSLG 16-10 trial participants and historical controls

	AMLSG 16-10 n = 440	Historical controls n = 415	p-value
Age, y Median (range)	54.1 (18-70)	54.1 (18-70)	<0.001

Female, n (%)	249 (57)	222 (54)	.37
ECOG PS, n (%) 0 1 2	 169 (38) 218 (50) 53 (12)	 92 (22) 255 (62) 68 (16)	<0.0001
WBC, 10^9/L Median (range)	 41.8 (0.3-420)	 44.8 (0.2-439)	.40
Haemoglobin, g/dL Median (range)	 9.0 (4.1-18.1)	 9.0 (3.1-16.6)	.79
Platelets, 10^9 /L Median (range)	 59 (5-681)	 58 (6-734)	.37
AML type, n (%) De novo Secondary Therapy-related Missing	 390 (89) 31 (7) 19 (4) 0	 396 (96) 6 (1) 12 (3) 1	<.0001
Cytogenetics, n (%) Intermediate I Intermediate II Adverse Missing	 285 (69) 101 (25) 26 (6) 28	 321 (78) 72 (17) 22 (5) 0	.02
FLT3-ITD, n (%) Allelic ratio <0.5 Allelic ratio ≥0.5	 196 (45) 242 (55)	 129 (44) 165 (56)	.67
Mutated *NPM1*, n (%) Yes No Missing	 266 (60) 174 (40) 0	 229 (56) 178 (44) 8	.24

Abbreviations: ANC: absolute neutrophil count; AML: acute myeloid leukaemia; ECOG PS: Easter Cooperative Oncology Group Performance Score; FLT3: FMS-like tyrosine kinase 3; ITD: internal tandem duplication; *NPM1:* nucleophosmin 1; WBC: white blood cell.

Unlike RATIFY, the trial included patients aged 60 years and older and a population with an age distribution that is more reflective of UK practice (18-60 years, n= 312 [71%]; 61-70 years, n=128 [29%]). Although conducted in Germany and Austria, the investigated treatments were generally in line with standard UK practice, and measured outcomes that broadly followed standard definitions, including CRi. Unlike QuANTUM-First and RATIFY RCTs, AMLSG 16-10 was a single-arm, open-label trial. Results were compared with a historical cohort of 415 patients treated without midostaurin in five prior AMLSG trials of standard chemotherapy conducted between 1993 and 2009[38-42] using a double-robust adjustment strategy of propensity score weighting and covariate adjustment (including age, sex, WBC count, bone marrow blasts, *NPM1* status and *FLT3-ITD* allelic ratio) in a (weighted) Cox PH model. Results for the midostaurin arm were also compared with 273 patients (18-59 years) with *FLT3-ITD+* treated on the placebo arm of RATIFY trial for OS.

Compared with the historical control group, midostaurin led to better OS (HR 0.56; 95% CI 0.47 to 0.68), CR (HR 0.75; 95% CI 0.59 to 0.96) and CIR (HR 0.37; 0.29 to 0.48). Midostaurin also led to

better OS (HR 0.71; 95% CI 0.56 to 0.90) when compared with the subset of *FLT3-ITD+* patients in the placebo arm of the RATIFY trial. Further results are presented in Section 3.6.1.2

EAG Comments

The AMSLG 16-10 includes a population that includes patients up to the age of 70 years, which is broadly reflective of NHS practice. The EAG has serious concerns about the conduct of the AMSLG 16-10 and considers it to be at high risk of bias, notably due to the risk of confounding (see Appendix Table 45). Statistically significant imbalances were reported between the AMSLG 16-10 population and historical controls for age, performance status, AML-type and cytogenetic risk. The EAG considers the statistical methods used to adjust for imbalances between AMLSG 16-10 and control groups appropriate. However, there remains a high risk of residual confounding bias due to the lack of adjusting for historical differences in practice and potential unobserved differences between the trial and older, control cohort populations, which may impact on the OS, CR and CIR comparisons.

3.3.2 Trial of sorafenib in the post-HSCT maintenance setting

As described in Section 2.3, sorafenib is commonly used in clinical practice as a maintenance therapy for AML post-HSCT, and therefore the EAG considers sorafenib to be a relevant comparator to quizartinib in this setting.

In response to clarification question A9, the company conducted an ITC of quizartinib and sorafenib post-HSCT maintenance therapies for the subset of patients with prior HSCT for *FLT3-ITD+* AML. The company identified two studies (SORMAIN[43] and a trial by Xuan et al. 2020 & Xu et al. 2022, hereafter referred to as Xuan (2020)[44, 45]) of sorafenib post-HSCT maintenance therapy, presented within the 2023 NHS evidence review of sorafenib maintenance for *FLT3-ITD+* AML following HSCT[19]. The company assessed the feasibility of conducting an ITC evaluating the efficacy of quizartinib and sorafenib in the post-HSCT maintenance setting. The feasibility assessment was conducted for OS and CIR and included both the SORMAIN and Xuan (2020) studies. Trial characteristics and patient baseline characteristics of the QuANTUM-First, SORMAIN and Xuan / Xu trials are summarised in Table 1 and Table 2 of the company's clarification response to question A9.

3.3.2.1 SORMAIN

SORMAIN is a placebo-controlled multi-centre RCT evaluating the efficacy and safety of sorafenib following HSCT and was conducted in Germany and Austria. A total of 83 adults with *FLT3-ITD+* AML were randomly assigned to receive sorafenib or placebo (1:1 ratio) for up to 24 months. Sorafenib doses were initiated at 200mg twice daily and increased incrementally up to 400mg twice daily. Treatment started between 60 and 100 days after HSCT and continued for up to 24 months. The trial measured RFS (primary endpoint) and OS (secondary endpoint). Relapse was defined as relapse or death, whichever occurred first.

Median follow-up was 41.8 months. The median RFS was not reached in the sorafenib group and was 30.9 months in the placebo group. The HR for relapse or death showed a statistically significant result favouring sorafenib over placebo (HR 0.39 [95% CI, 0.18 to 0.85]). The 24-month RFS probability was statistically significantly higher for sorafenib compared with placebo (85.0% vs. 53.3%; HR 0.26 [95% CI, 0.10 to 0.65]). Median OS was not reached in either arm; the 24-month OS probability was numerically higher for sorafenib but not statistically significant (90.5% vs. 66.2%; HR 0.52 [95% CI 0.24 to 1.11]). The trial reported no important safety signals and sorafenib was deemed to be well-tolerated; there were no sorafenib treatment-related deaths.

EAG Comments

The EAG found SORMAIN to be at low risk of bias overall (See Appendix Table 44). The company did not provide a formal quality assessment of SORMAIN. However, they noted that due to difficulties in recruitment, the final number of participants included in the trial represented 44% of its targeted sample size, and that the trial was therefore underpowered. The EAG agrees that the relatively small sample size of SORMAIN is a limitation. However, the achieved sample size did not prevent the trial from yielding effect estimates with sufficient power to show a clinically meaningful and statistically significant effect favouring sorafenib over placebo for relapse and RFS. Randomisation methods were reported and appeared broadly appropriate; key prognostic factors (WBC count, cytogenetic risk) were generally balanced at baseline although the proportion of females was higher in the sorafenib arm compared with placebo (58% vs. 43%). Long-term benefits of sorafenib are uncertain due to the limited follow-up duration of the trial. Eligibility criteria of the SORMAIN trial was restricted to patients who had a achieved a CR following HSCT. The applicability of the trial results to patients without CR post-HSCT, who may also be eligible to sorafenib in practice is uncertain,[19] although clinical advice to the EAG indicated that this would likely be a very small subset of patients.

3.3.2.2 Xuan (2020) & Xu (2022)

The study by Xuan (2020) is an open-label, phase 3, randomised multi-centre trial comparing sorafenib maintenance in China. A total of 202 adults aged 18-60 years with *FLT3-ITD*+ AML undergoing HSCT were randomly allocated to receive sorafenib (400mg twice daily) or no maintenance treatment (1:1 ratio). Eligible patients had CRc before and after transplantation and had haematopoietic recovery within 60 days post-transplantation. Treatment started between 30 and 60 days after HSCT and continued up to 180 days post-HSCT. Approximately 57% of patients also received sorafenib pre-transplant. Median duration of sorafenib treatment was 19 weeks. The trial measured CIR (primary endpoint) and OS.

Median follow-up post-transplantation was 21.3 months. The 1-year CIR rate was 7.0% in the sorafenib group vs. 24.5% in the control group (HR 0.25, 95% CI 0.11 to 0.57). Median OS was not

reached in either arm; the OS difference between arms was statistically significant (HR 0.48, 95% CI 0.27 to 0.86). Sorafenib was generally well tolerated and there were no sorafenib treatment-related deaths.

EAG Comments

Although the company did not conduct a formal quality assessment of the Xuan (2020) trial, they highlighted a number of limitations with regards to the generalisability of the Xuan (2020) study to UK practice, including: a significantly lower age for Xuan (median 35 years, age range 18-60 years); a relatively low rate of participants with *NPM1* mutations (29%, versus 43% in QuANTUM-First); a high proportion of participants receiving sorafenib prior to HSCT, which is not reflective of UK practice; the applicability of the Chinese setting and the Chinese population to the UK; and the requirement to be in CRc before and after transplant to undergo maintenance therapy which does not reflect UK practice. The EAG broadly agrees with the company that the Xuan (2020) trial has limited applicability to the UK setting; in addition, the open-label nature of the trial raises some concerns, as knowledge of the intervention by the trial investigators and participants may have influenced management decisions, including additional AML therapy (see Appendix Table 44 for further details).

3.4 Critique of the comparability of trials included in the indirect treatment comparisons

3.4.1 Quizartinib vs. midostaurin (all treatment phases)

As described in Section 2.3, the decision problem presented within the CS is limited to midostaurin as the only comparator to quizartinib in all treatment phases. In the absence of a direct comparison of the efficacy and safety of quizartinib + standard chemotherapy versus midostaurin + standard chemotherapy (hereafter referred to as quizartinib versus midostaurin), the company carried out a series of ITCs.

As described in CS Section 2.9 and Appendix D of the CS, the company considered that only two trials were eligible for inclusion in the ITCs; the QuANTUM-First trial and the RATIFY trial. Data from a subgroup analysis of the RATIFY trial including only patients (n=555) with the *FLT3-ITD* mutation[36] was used in the ITCs.

Trial characteristics, outcome definitions and patient baseline characteristics of the QuANTUM-First and RATIFY trials relevant to the ITCs are summarised in Appendix Table 43. Quality assessments of the trials are provided in CS Section 2.5 and Appendix D.1.4, and further discussed in Section 3.1.4.

The company present ITCs for OS, CR and CIR, the latter as a proxy for RFS. The company state that it was not feasible to indirectly compare other efficacy endpoints, due to differences in definitions of efficacy endpoints across the two trials. The company also state that an ITC of HRQoL comparing quizartinib and midostaurin is not feasible due to the lack of HRQoL data reported in the RATIFY trial (response to clarification question A19). The company provide an overview of AEs in the safety populations of the QuANTUM-First and RATIFY trials (response to clarification question A19); AE rates were not presented separately for the *FLT3-ITD*+ subgroup of the RATIFY trial. The company conclude that quizartinib has, at worst, a similar AE profile to midostaurin, with worse gastrointestinal side effects expected on midostaurin according to clinical expert advice. Due to 'limited impact of adverse events on cost-effectiveness outcomes,' an ITC of AEs was not conducted.

3.4.1.1 EAG Comments

The EAG notes several important issues regarding differences in trial design and outcome data between the QuANTUM-First and RATIFY trials which impacts upon the interpretation of the ITCs results and their generalisability to NHS clinical practice.

Issue 1: Time frame of the QuANTUM-First and RATIFY trials

A key difference between the trials which impacts upon the interpretation of the ITC results and is unresolvable is the different time frames during which the QuANTUM-First and RATIFY trials were

conducted. The study-start and primary completion dates for the RATIFY trial were April 2008 and July 2016 respectively, compared with Sept 2016 and Aug 2021 for the QuANTUM-First trial. Clinical advice to the EAG indicated that improvement in clinical practice over time, including better supportive care, improved management of chemotherapy toxicity and increased availability of transplant donors and criteria for transplant eligibility have improved treatment outcomes for people with AML over time. Therefore, the results of the RATIFY trial are likely not to be generalisable to current NHS clinical practice, and the comparability of the results of the RATIFY trial and the QuANTUM-First trial is uncertain.

Issue 2: Age eligibility criteria in the QuANTUM-First and RATIFY trials

A key difference in eligibility criteria of the two trials is that patients aged 18 to 75 years were eligible for enrolment in the QuANTUM-First trial, whereas the eligibility criteria of the RATIFY trial were 18-59 years (CS, Document B, Table 21). This difference in eligibility criteria has resulted in large differences in the age distributions across the two trials (CS, Document B, Table 23) which has impacted on the applicability of the results from the MAICs conducted by the company (Section 3.5.1.2 and Section 3.5.1.6).

Issue 3: Availability of baseline characteristics in the QuANTUM-First and RATIFY trials

A number of baseline characteristics could not be compared across the trials, where one of the trials did not record the characteristics, or the characteristic was recorded in a different format in the two trials. These characteristics included race, ECOG PS, geographic region, WBC count, ELN risk group, cytogenetic risk status and abnormal karyotypes. Consequently, the comparability of the trial populations in terms of these characteristics is unknown. The lack of comparable data on a number of characteristics considered to be treatment effect modifiers across the two trials has also impacted on the population-adjusted ITCs conducted by the company (see Section 3.5.1.1).

Issue 4: Data on remission

The two trials collected different data relating to the outcome of CR (CS, Document B, Table 21). QuANTUM-First recorded CR as well as CRi (i.e., CR with incomplete platelet recovery or incomplete neutrophil recovery), allowing calculation of CRc rates (i.e., the percentage of patients achieving CR or CRi after induction), whereas RATIFY recorded CR only. Clinical advice to the EAG indicated that CRc rates are used to measure response to induction therapy in current NHS clinical practice, in line with current ELN[23] and ESMO guidelines[25]. The company could only perform ITCs for CR, and not for CRc, due to the availability of outcome data in the RATIFY trial. Clinical advice to the EAG indicated that the rates of CRi, and therefore CRc, cannot be assumed to be equivalent for quizartinib and midostaurin, as midostaurin is not considered to be myelosuppressive. Therefore, a higher CRi rate may be expected with quizartinib compared to midostaurin. The EAG considers that this issue is unresolvable within the ITCs of remission from the QuANTUM-First and

RATIFY trials, but notes that an indirect comparison of quizartinib and midostaurin for CRc may be possible using data from the AMLSG 16-10 trial [34]of midostaurin, which may partially resolve this issue (see Section 3.6.1.2).

Issue 5: HSCT rates in the QuANTUM-First and RATIFY trials and lack of adjustment for HSCT in ITCs of OS and CIR

There are a number of differences in the trial design and procedures which may have implications for the respective HSCT rates within the trials (CS, Document B, Table 21). This may also have implications for the interpretation of OS and CIR across the two trials as both outcomes will be confounded by HSCT rates. In the QuANTUM-First trial, HSCT was protocol-specified during the consolidation phase, and also during the maintenance phase if certain protocol-defined criteria were met, although non-protocol-specified HSCT was also permitted (CS, Section B.2.6.3). This contrasts with the RATIFY trial where HSCT was not mandated in the protocol and was performed at investigator discretion. Differences in the response data collected in the trials (i.e. CR or CRc) as well as changes in practice may have also impacted on the HSCT rates within the two trials.

As described in Section 2.2.3, clinical advice to the EAG noted that MRD analysis is commonly used in current UK clinical practice to determine eligibility for transplant in *NPM1* mutated patients. The percentage of patients achieving CR and CRc with *FLT3-ITD* MRD negativity following induction therapy was collected and assessed within a post-hoc analysis in QuANTUM-First trial (CS, Section B.2.6.4), suggesting longer OS on quizartinib compared to placebo, particularly for patients who were MRD positive prior to HSCT.[46] However, MRD analysis was performed using next-generation sequencing, which has been regarded as an exploratory method which could have limited sensitivity for detecting MRD in AML by the ELN.[23]

Furthermore, MRD analysis was not used within treatment decisions including HSCT uptake during the QuANTUM-First trial (response to clarification question A8) and MRD positivity and negativity rates were not collected at any point during the RATIFY trial. Therefore, the generalisability of the HSCT rates within both of the trials, without the use of MRD analysis to guide treatment decisions, to current UK clinical practice is limited.

An analysis of OS censored at the time of HSCT was available from the QuANTUM-First trial (CS, Figure 6), but not for the *FLT3-ITD*+ subgroup of the RATIFY trial. Neither trial censored nor adjusted the analyses of CIR to account for patients receiving HSCT. Therefore, any differences in HSCT rates across the trials would confound the ITCs of OS and CIR.

The company argue that as the transplantation rate was higher in the RATIFY trial compared to the QUANTUM-First trial, this would result in favourable durable remission and survival for midostaurin (compared to quizartinib) and is therefore the lack of any adjustment is conservative (CS, p109). The

EAG considers that the protocol-specified HSCT and non-protocol specified HSCT (i.e. total HSCT rate) in the QuANTUM-First trial ITT population (53.7% in the quizartinib group and 47.2% in the placebo group; CS, Document B, Table 20) is comparable to the total HSCT rate in the RATIFY trial ITT population (59% in the midostaurin group and 55% in the placebo group), and the total HSCT rate in the RATIFY trial *FLT3-ITD+* subgroup is unknown.

Furthermore, as well as the HSCT rate, the time that HSCT was performed has an impact on survival analysis for OS, as demonstrated by differences in OS between patients with HSCT in first complete remission (CR1) and outside of CR1 in a post-hoc analysis of the QuANTUM First trial (response to clarification question A3c, Figure 3) and also within the RATIFY trial ITT population (Figure S3A of the Stone *et al.*[33] publication of the RATIFY trial, stratified by *FLT3* subtype) and would likely also impact on analyses of CIR.

While it is likely that bias is present within the ITCs of OS and CIR due to the lack of adjustment for HSCT, the EAG is uncertain regarding the magnitude and direction of bias introduced into the OS and CIR ITCs and considers that this issue is unresolvable.

Issue 6: Violation of proportional hazards

The PH assumption appears to be violated for OS in both the QuANTUM-First trial (response to clarification question A6a, further discussed in Section 3.2.4.1) and the *FLT3-ITD+* subgroup of the RATIFY trial (response to clarification question A10a). Furthermore, although there is no evidence of violation of the PH assumption for CIR (response to clarification questions A6b and A10b), the use of population-adjusted ITC methods implies the existence of covariate effects which in turn, implies that hazards are non-proportional for both OS and CIR. Therefore, the interpretation of constant HRs estimated from the ITCs of OS and CIR is limited, and their application within economic modelling is inappropriate for decision making (see Issue 4 in Section 3.5.1.6 for further discussion).

Other issues

There are a number of differences between the designs and procedures of QUANTUM-First and RATIFY trials as well as differences in patient baseline characteristics. The EAG notes the following, but does not consider that these differences have any meaningful impact on the ITC results:

- The RATIFY trial included patients with either *FLT3-ITD+* or *FLT3-TKD+* mutations, whereas QuANTUM-First included patients with a *FLT3-ITD+* mutation only. Randomisation in the RATIFY trial randomisation was stratified by *FLT3* subtype (TKD, ITD_{low} or ITD_{high}). However, baseline imbalances in terms of sex, ELN risk group, karyotype, and *NPM1* mutation are present between the midostaurin and placebo arms of the RATIFY *FLT3-ITD+* subgroup (CS, Document B, Table 23).

- The choice of induction chemotherapy and chemotherapy regimen for a second induction (CS, p82) differed in the two trials and maintenance therapy with midostaurin in the RATIFY trial was permitted for up to 12 months whereas maintenance therapy with quizartinib was permitted in the QuANTUM-First trial for up to three years (CS, Document B, Table 21). Clinical advice to EAG is that it is reasonable to consider the efficacy of the chemotherapy options across the two trials to be equivalent and that the extended duration of quizartinib maintenance therapy may result in beneficial clinical outcomes
- The median follow-up in the ITT population of the QuANTUM-First trial was 39.2 months, whereas the median follow-up among those who survived in the RATIFY trial *FLT3-ITD+* subgroup was 59 months (CS, Document B, Table 21). Due the differences in definitions of median follow-up presented across the trials, the EAG is uncertain whether there are any important differences in the extent of follow-up and the maturity of the data from the two trials.
- A higher proportion of patients with the *FLT3-ITD* mutation had a high allelic ratio (>0.5) and a higher median platelet count in the RATIFY trial compared to the QuANTUM-First trial (CS, Document B, Table 23). Clinical advice to the EAG indicated that patients with a high allelic ratio have a worse prognosis, but that differences in platelet count at baseline are less important.
- The two trials used different stratification factors (CS, Document B, Table 21), which may have resulted in different distributions of baseline characteristics. Differences in the distribution of baseline characteristics across the trials may impact on the overlap of the population distributions and therefore the stability of estimates from population-adjusted ITCs (see Section 3.5.1.1)

The EAG acknowledges that that due to differences in the definitions of outcomes collected in the RATIFY trial compared to the QuANTUM-First trial, it is not possible to conduct meaningful ITCs of efficacy outcomes such as EFS, RFS, CRc and transplant rates, nor of HRQoL. The EAG notes the following regarding the definitions of OS, CIR, and CR:

- The definition of OS was consistent between the QuANTUM-First and RATIFY trials (CS, Document B, Table 22) and the standard definition of OS used within clinical practice.
- The definitions of CIR were mostly consistent between the trials, with minor differences in the definition of a relapse following CR (CS, Document B, Table 22). Within both trials, CIR was measured as time from the date of first CR to relapse, with death due to AML (among patients achieving CR) modelled as a competing risk.
- Both trials allowed for CR to be achieved within two induction cycles, i.e., a period of up to 120 days (CS, Document B, Table 21). Clinical advice to the EAG indicated that allowing 120 days to achieve CR is generous and typically within NHS clinical practice, a cut-off of 42 days to achieve CR is applied. Although the relative difference in CR rates would not be impacted as the cut-off 120 days is used in both of the QuANTUM-First and RATIFY trials, the absolute CR rates in the

two trials may be an overestimate of CR rate within NHS clinical practice, given the extended cut-off time to achieve CR.

Different rates of AEs were applied within the economic model based on the rates reported in the QuANTUM-First and RATIFY trials. The EAG considers that an ITC could have provided some additional value over a naïve comparison of the AE rates of quizartinib and midostaurin, particularly relating to the company claim that as a second generation FLT3 inhibitor, quizartinib may limit off-target effects and could reduce the drug toxicity and adverse effects to patients associated with first-generation inhibitors, such as midostaurin (see Section 2.2.2).

3.4.2 Quizartinib vs. sorafenib (post-HSCT maintenance therapy)

As discussed in Section 3.3.2, the company performed a feasibility assessment conducting ITCs of quizartinib and sorafenib post-HSCT maintenance therapies for OS and CIR including either of SORMAIN and Xuan (2020) trials.[43, 44]

The company's feasibility assessment noted a number of differences in the trial design and patient characteristics between the QuANTUM-First and the Xuan (2020) trials. Due to these differences, and due to limited available patient baseline characteristics from the Xuan (2020) trial for comparison with the QuANTUM-First trial, the company considered that an ITC using evidence from the SORMAIN trial, and the QuANTUM-First trial would be the most robust. The company notes that, unlike the QuANTUM-First trial, the SORMAIN trial required patients to have achieved CR post-HSCT to receive sorafenib maintenance treatment. The SORMAIN trial is also underpowered, discontinuing recruitment early after 83 patients (44% of the target sample size) had been randomised, due to difficulties in recruitment.

An additional study[47] identified randomised patients to sorafenib or placebo plus intensive chemotherapy for induction and consolidation phases and excluded patients who had received HSCT from receiving sorafenib maintenance therapy, as it was not the standard of care at the time when the study commenced. As this study does not provide evidence of sorafenib maintenance therapy post-HSCT, it was excluded from the ITCs.

3.4.2.1 EAG Comments

The EAG agrees with the company exclusion of the Loo *et al*[47] trial from the ITCs, and also that using evidence from the SORMAIN trial (and the QuANTUM-First trial) provides a more robust comparison than using evidence from the Xuan / Xu trial.

The EAG also agrees with the company that despite the SORMAIN trial being the most robust source of sorafenib post-HSCT maintenance therapy evidence available to inform an ITC, the limited sample size of the SORMAIN trial is a major limitation of the ITCs between quizartinib and sorafenib.

3.5 Critique of the indirect treatment comparison

3.5.1 Quizartinib vs. midostaurin (all treatment phases)

To account for the differences in patient baseline characteristics in the QuANTUM-First and RATIFY trials, as highlighted in CS, Section B.2.8.2, the company conducted population-adjusted ITCs to compare the efficacy of quizartinib vs midostaurin across the induction, consolidation and maintenance phases of treatment. The ITCs conducted by the company are presented in CS, Section B.2.8.4 and Appendix M, and additional MAIC report[48])

For the outcomes of OS, CR and CIR following CR, the company presented:

- Anchored matching adjusted indirect comparisons (MAICs), using the common placebo + standard chemotherapy as an anchor (CS, Section B.2.8.4 and a MAIC report[48])
- A Multilevel Network Meta Regression (ML-NMR)(CS, Appendix M)
- Naïve comparisons without population adjustment (CS, Section B.2.8.4)

A network diagram for the ITCs comparing quizartinib and midostaurin is provided in CS, Figure 15.

All ITCs were conducted using individual participant data (IPD) from the QuANTUM-First trial, and aggregate data, including digitised KM data from the *FLT3-ITD*+ subgroup of the RATIFY trial.

The results of the MAICs were used to inform the company's base case in the economic model, and the results of the ML-NMR were used in a scenario analysis for the economic model. Results of naïve comparisons did not contribute to the company's economic analyses and served only as a reference to assess whether performing population-adjusted ITCs has impacted upon the treatment effects of quizartinib versus midostaurin.

3.5.1.1 Selection of treatment effect modifiers

The company's first step of the population-adjusted ITCs was to confirm the presence of treatment effect modifying variables within the QuANTUM-First and RATIFY trials (CS, Section B.2.8.3). Potential treatment effect modifiers (TEMs) were identified firstly through a literature review of the OS subgroup analyses from publications of the RATIFY trial, then through an 'interaction analysis' of the QuANTUM-First OS data. Univariate Cox regression analyses were conducted using interaction terms of the baseline characteristics with treatment; characteristics showing significant association with treatment at the 75% significance level ($p \leq 0.25$) were flagged for further consideration. Finally, the list of TEMs selected through discussion with three clinical experts. The TEMs considered for inclusion in the population-adjusted ITCs are summarised in Table 8.

Table 8 Treatment effect modifiers considered for inclusion in population adjusted ITCs

Treatment effect modifier	Identified by:			Included within Population Adjusted ITCs?
	Literature review[a]	Interaction analysis[b]	Clinical Experts	
Adjusted				
Platelet count	No	No	Yes	Yes: MAIC (base case) and ML-NMR
Sex	No	No	Yes	Yes: MAIC (base case) and ML-NMR
Age	Yes	No	Yes	Yes: MAIC (base case) and ML-NMR
NPM1 mutation status	Yes	Yes	Yes	Yes: MAIC (base case) and ML-NMR
FLT3-ITD allelic ratio	No	Yes	Yes	Yes: MAIC (scenario analysis only)[c]
Bone marrow blasts	No	Yes	Yes	Yes: MAIC (scenario analysis only)[d]
Not adjusted				
ELN risk	Yes	No	No	No: data not available from QuANTUM-First
Cytogenetic risk	No	Yes	Yes	No: data not available from RATIFY
WBC count	No	No	Yes	No: data collected in different formats in QuANTUM-First and RATIFY trials
ANC	No	No	Yes	No: data not available from RATIFY
Geographical region	No	No	Yes	No: data not available from RATIFY
Race	No	No	Yes	No: data not available from RATIFY and ranked as low importance by clinical experts

Source: Document B, CS, Table 25

Abbreviations: ANC: absolute neutrophil count; ELN: European LeukemiaNet; ESS: effective sample size; *FLT3-ITD*: FMS-like tyrosine kinase 3 internal tandem duplication; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; ML-NMR: multilevel network meta-regression; WBC: white blood count

a Literature review of the OS subgroup analyses from publications of the RATIFY trial.
b Univariate Cox regression analyses were conducted using interaction terms of the baseline characteristics with treatment and characteristics showing statistically significant association with treatment at the 75% significance level ($p \leq 0.25$) were flagged for further consideration.
c Excluded from the base case MAIC due to ESS when including this characteristic of less than 50% of the original sample size, included only in a scenario analysis.
d Excluded from the base case MAIC as this characteristic was ranked low on the importance scale (of potential treatment effect modifiers) by the clinical experts.

3.5.1.2 MAIC methods

The company approach to the anchored MAIC is reported in CS, Section 2.8.4 and in an MAIC report[48]. The company employ the methods outlined in TSD DSU 18[49].

The approach of a MAIC, using inverse propensity score weighting (IPSW), reweights patient characteristics identified as TEMs within the IPD from the trial of the intervention of interest (i.e. quizartinib in the QuANTUM-First trial) to create a patient population which aligns with that of the comparator (i.e. midostaurin in the RATIFY trial FLT3-ITD subgroup, a 'RATIFY-like' population). Reweighting results in a loss of statistical information, and an 'effective sample size' (ESS) which is

lower than the original sample size of the trial population. Large reductions in ESS may indicate poor overlap between the trial populations being matched, resulting in unstable MAIC estimates. The company restricted the number of TEMs reweighted initially, ranked according to order of importance by clinical experts, to maintain an ESS of at least 50% within the base case analysis. The company also conducted scenario analyses adding single additional TEMs, ranked as lower importance by clinical experts, into the IPSW model and allowing the ESS to fall below 50%.

Due to the differences in the eligibility criteria relating to age within the two trials, in order to match the QuANTUM-First trial IPD to the RATIFY trial aggregate data, the company restricted the QuANTUM-First ITT population to the population < 60 years old (n=331, 61.4% of the ITT population). Therefore, it was the QuANTUM-First < 60 years population which was reweighted to be comparable with a 'RATIFY-like' population.

Following reweighting, treatment effects for OS, CR and CIR (i.e. log HRs or ORs) for the indirect comparison of quizartinib vs midostaurin are estimated using a Bucher equation[50] (CS, p94) with corresponding standard errors and 95% confidence intervals (CIs) calculated using a robust sandwich variance estimation.

Naïve comparisons

To act as a reference for the MAIC, the company also performed naïve comparisons of quizartinib vs midostaurin using outcome data from the QuANTUM-First <60 population and the RATIFY *FLT3-ITD*+ subgroup.

3.5.1.3 MAIC results

A summary of the patient baseline characteristics of the adjusted QuANTUM-First <60 years population following reweighting of age, sex, *NPM1* mutation status, platelet count and *FLT3-ITD* allelic ratio >0.5 is provided in CS, Document B, Table 26. The ESS of the QuANTUM-First <60 years population reduced to [redacted] when reweighted for platelet count, sex, age and *NPM1* mutation status, and fell to [redacted] reweighting for *FLT3-ITD* allelic ratio >0.5 was also added. Following reweighting, imbalances remained between the trial populations in median platelet count and *FLT3-ITD* allelic ratio >0.5, the latter was included only in scenario analyses. As the median platelet count of patients was higher in the RATIFY trial compared to the QuANTUM-First <60 years population, even after reweighting, patients with higher platelet counts were comparatively underrepresented in the QuANTUM-First <60 years population and therefore given higher propensity score weights when matching (CS, Figure 16). The company highlight this imbalance in platelet count as a potential risk of bias in the MAICs and consider that the patients with

higher weights could have influenced the matched outcomes significantly (CS, Document B, pp.108-109).

Results of the MAICs (and the naïve comparisons as a reference) are reported in CS, Document B, Section 2.8.5 and the MAIC report. The results for OS, CR and CIR are summarised in Table 9.

Table 9 MAIC and naïve comparison of quizartinib and midostaurin: results for OS, CR and CIR following CR

Analysis	Comparison	OS	CR	CIR
		HR (95% CI)[a]	OR (95% CI)[b]	HR (95% CI)[a]
QuANTUM-First <60, unadjusted	Quizartinib vs. placebo	0.68 (0.50 to 0.94)	1.04 (0.67 to 1.60)	0.49 (0.28 to 0.86)
QuANTUM-First <60 weighted	Quizartinib vs. Placebo	0.65 (0.42 to 1.00)	1.14 (0.62 to 2.12)	0.34 (0.17 to 0.66)
RATIFY *FLT3-ITD* subgroup	Midostaurin vs. Placebo	0.79 (0.59 to 1.06)	1.25 (0.79 to 1.99)	0.80 (0.56 to 1.15)
Naïve comparison	Quizartinib vs. Midostaurin	0.87 (0.56 to 1.34)	0.83 (0.44 to 1.56)	0.61 (0.31 to 1.19)
MAIC	Quizartinib vs. Midostaurin	0.82 (0.48 to 1.39)	0.92 (0.42 to 1.97)	0.42 (0.20 to 0.91)

a HR<1 favours the first treatment over the second treatment in the comparison.
b OR>1 favours the first treatment over the second treatment in the comparison.
Source: CS, Document B, Tables 27-29
Abbreviations: CI: confidence interval; CIR: cumulative incidence of relapse; CR: complete remission; *FLT3-ITD*: FMS-like tyrosine kinase 3 internal tandem duplication; ITT: intention to treat; HR: hazard ratio; MAIC: matching adjusted indirect comparison OR: odds ratio; OS: overall survival

The MAIC showed numerically favourable outcomes for quizartinib compared to midostaurin which were not statistically significant for OS (HR 0.82, 95% CI: 0.48 to 1.39), but a numerically favourable outcome for midostaurin compared to quizartinib which were not statistically significant for CR (OR 0.92, 95% CI 0.42 to 1.97). Naïve comparisons for OS and CR provided numerically similar results.

The MAIC showed a statistically significant and numerically large advantage for quizartinib compared to midostaurin for CIR following CR (HR 0.42, 95% CI: 0.20 to 0.91), whereas the naïve comparison indicates a smaller numerical advantage to quizartinib compared to midostaurin which is not statistically significant (HR 0.61, 95% CI: 0.31 to 1.19). Inspection of adjusted and unadjusted cumulative incidence curves for CIR for the QuANTUM-First <60 years population (CS, Figure 18) shows a substantial increase in CIR following CR for patients in the placebo group following adjustment, which is not observed for patients in the quizartinib group. The company state that the 'upwards shift' of the placebo curve is due to 'placebo patients with a higher weight experiencing relapse events' (CS, p100; response to clarification question A13).

The company present two scenario analyses, separately adding baseline *FLT3-ITD* allelic ratio >0.5 and bone marrow blasts to the four TEMs already included in the MAICs. Results of the scenario

analyses (CS, Document B, Table 33) were numerically similar for OS and CIR. For CR, the direction of effect (i.e. a numerical advantage to quizartinib compared to midostaurin or vice versa) varied across the base case and the scenarios. However, no results were statistically significant, and 95% CIs were wide, particularly for the scenario including bone marrow blasts as a TEM, indicating uncertainty within the indirect comparison of quizartinib versus midostaurin for CR.

3.5.1.4 ML-NMR methods

To overcome the fundamental limitation of MAICs in this context, which constrain the 'target' population to that of the comparator study (i.e. RATIFY), the company conducted ML-NMR which provides additional flexibility to generate population-averaged ITC estimates which are applicable to any specified target population (i.e. a 'QuANTUM-First ITT like' population).

The company approach to the ML-NMRs is reported in the CS, Section B.2.8.7 and Appendix M. The company employ the methods outlined by Phillipo et al[51-53] and implement the ML-NMRs using the multinma[54] package in R. Statistical code is provided in response to clarification question A15.

The general approach of the ML-NMRs is to fit individual patient level regression models for each outcome of interest to the IPD from the QuANTUM-First trial (ITT population) and then mathematically integrate that model over the RATIFY *FLT3-ITD+* population to form an aggregate level model (CS, Appendix M.1.1.1). The same four TEMs adjusted for within the MAICs were included as covariates within the ML-NMR models (i.e. platelet count, age, sex, *NPM1* mutation status). As only two trials were included within the ML-NMRs, IPD for the QuANTUM-First trial and aggregate data for the RATIFY trial *FLT3-ITD+* population, data were insufficient to estimate independent effect modifier interaction terms for each treatment. Therefore, it was necessary to assume shared-effect modification between quizartinib and midostaurin. Due to this assumption, the estimated indirect relative effect sizes for the comparison of quizartinib and midostaurin are the same across different populations. In other words, the relative effect sizes estimated for quizartinib versus midostaurin within the ML-NMR are applicable to both a 'QuANTUM-First like' population and also to a 'RATIFY-like' population.

The company modelled binary outcome CR using a Bernoulli distribution with a logit link function (CS, Appendix M.1.1.4). For time-to-event outcomes OS and CIR, the company considered parametric PH models, and a PH model with cubic M-splines on the baseline hazard (CS, Appendix M.1.1.3) and compared model fit using the approximate leave-one-out validation information criterion (LOOIC) and expected log predictive density (ELPD), with the highest ELPD and lowest LOOIC demonstrating best fitting model (CS, Appendix M.1.1.5). For OS and CIR, the company selected the model with cubic M-splines on the baseline hazard for inference, as the best fitting model according to LOOIC and ELPD (CS, Appendix M; Table 4 and Table 7).

Despite evidence of PH violation for OS in both the QuANTUM-First trial (response to clarification question A6a) and the RATIFY *FLT3-ITD+* population (response to clarification question A10a), the company did not assess models which allowed relaxation of the PH assumption (e.g., accelerated failure time models).

The company also considered fixed and random effects ML-NMR models, comparing model fit in terms of residual deviance and deviance information criterion (DIC), and assessed convergence of model parameters to determine model stability. The company selected fixed-effect models for inference, due to similar DIC statistics and due to limited data available from two trials to estimate the between-study heterogeneity parameters.

3.5.1.5 ML-NMR results

A summary of the patient baseline characteristics of the covariates (i.e., age, sex, *NPM1* mutation status, platelet count) from the QuANTUM-First ITT population and RATIFY *FLT3-ITD+* subgroup included in the ML-NMR are provided in CS, Appendix M, Table 1. Further information regarding covariate adjustment is provided in response to clarification question A14.

Results of the fixed-effect ML-NMRs are reported in CS, Appendix M, Tables 2, 5, and 8, and in response to clarification question A16 (Table 11, Table 12, and Table 13). The results for OS, CR and CIR in a 'QuANTUM-First ITT like' population are summarised in Table 10.

Table 10 Fixed effect ML-NMR of quizartinib and midostaurin: results in a QuANTUM-First ITT like population for OS, CR and CIR following CR

Analysis	Comparison	OS	CR	CIR
		HR (95% CI)[a]	OR (95% CI)[b]	HR (95% CI)[a]
QuANTUM-First ITT population	Quizartinib vs. placebo	0.78 (0.62 to 0.98)	0.98 (0.70 to 1.37)	[redacted]
RATIFY *FLT3-ITD+* subgroup	Midostaurin vs. Placebo	[redacted]	1.25 (0.79 to 1.99)	[redacted]
QuANTUM-First-ITT like population[c]	Quizartinib vs. placebo	[redacted]	[redacted]	[redacted]
	Midostaurin vs. Placebo	[redacted]	[redacted]	[redacted]
	Quizartinib vs. Midostaurin	[redacted]	[redacted]	[redacted]

a HRs are population-average conditional HR estimates. HR<1 favours the first treatment over the second treatment in the comparison.
b ORs are population-average conditional OR estimates. OR>1 favours the first treatment over the second treatment in the comparison.
c Population-average conditional effect estimates conditional upon the covariate (i.e., platelet count, age, sex, NPM1 mutation status) values of the QuANTUM-First ITT population
Source: CS, Appendix M, Table 2, Table 5 and Table 8 and response to clarification questions A5 and A16
Abbreviations: CI: confidence interval; CIR: cumulative incidence of relapse; CR: complete remission; *FLT3-ITD*: FMS-like tyrosine kinase 3 internal tandem duplication; ITT: intention to treat; HR: hazard ratio; ML-NMR: multilevel network meta-regression; OR: odds ratio; OS: overall survival

The ML-NMR results for the comparison of quizartinib and placebo in a 'QuANTUM-First ITT like' population for OS and CR are numerically very similar to those observed within the ITT population of the QuANTUM-First trial, as would be expected. The ML-NMR result for CIR suggests a larger, statistically significant advantage in a QuANTUM-First ITT like' population (HR [redacted], 95% CI: [redacted]) than is observed within the trial (HR [redacted], 95% CI: [redacted]), demonstrating the impact of covariate adjustment on CIR.

The ML-NMR results for the comparison of midostaurin and placebo in a 'QUANTUM-First ITT like' population, i.e. extrapolating the RATIFY FLT3-ITD+ subgroup results to an older population are variable. The ML-NMR result for OS (HR [redacted], 95% CI: [redacted]), is very similar to the observed result in the RATIFY *FLT3-ITD*+ subgroup (HR [redacted], 95% CI: [redacted]), whereas a greater numerical advantage to midostaurin over placebo is estimated by the ML-NMR for CR (OR [redacted], 95% CI: [redacted]) compared to the observed result in the RATIFY *FLT3-ITD*+ subgroup (OR [redacted], 95% CI: [redacted]), although neither is statistically significant. A numerical, but not statistically significant, advantage for midostaurin compared to placebo was observed in the RATIFY *FLT3-ITD*+ subgroup for CIR (HR [redacted], 95% CI: [redacted]), whereas no difference between midostaurin and placebo was estimated by the ML-NMR (HR [redacted], 95% CI: [redacted]).

The ML-NMR showed no statistically significant differences between quizartinib compared to midostaurin for OS and CR, with a slight numerical advantage for midostaurin over quizartinib indicated for OS (HR [redacted], 95% CI: [redacted]) and a larger numerical advantage for midostaurin over quizartinib for CR (OR [redacted], 95% CI: [redacted]). The ML-NMR showed a statistically significant and numerically large advantage for quizartinib compared to midostaurin for CIR (HR [redacted], 95% CI: [redacted]).

The company present predicted population-average incidence of relapse curves for CIR and survival curves for OS on each treatment (i.e. quizartinib, midostaurin or placebo) in CS, Appendix M, Figure 1, and Figure 3 respectively, and population-average marginal hazards on each treatment for CIR and OS in CS, Appendix M, Figure 2 and Figure 4 respectively.

The company consider that from visual inspection, the estimated survival curves are a good fit to the KM curves from each study and that the adjusted survival curves account for the differences in covariate distributions between treatment arms and are therefore reflective of the target population, i.e. QuANTUM-First ITT like' population. On the other hand, from visual inspection, the estimated incidence of relapse curves are not a good fit to KM curves from the QuANTUM-First study which the company attribute to low patient numbers and differences in prognostic factors in the QUANTUM-First and RATIFY studies (CS, Appendix M, Section M.1.2.2.3).

3.5.1.6 EAG comments

The EAG considers that the company seem to have correctly implemented the MAICs, with adequate population overlap as demonstrated by the ESS and few outliers with high weights due to imbalances in median platelet count between the trials, which remained after reweighting.

The EAG also considers that the company seem to have correctly implemented the ML-NMRs. Clinical advice to the EAG is that it is reasonable to assume that TEMs are the same for quizartinib and midostaurin, therefore the EAG considers that the assumption of shared effect modification is appropriate in these analyses.

Issue 1: Omission of TEMs due to lack of available data

The EAG considers that the company process for identifying TEMs was generally appropriate but notes that the unavoidable omission of many important TEMs due to lack of available data in the QuANTUM-First and RATIFY trials is a major limitation of the both the MAICs and the ML-NMRs which cannot be resolved. The clinical experts consulted by the company noted cytogenetic risk and WBC count as the 'most impactful' (CS, p91) omissions and clinical advice to the EAG also highlighted these two variables as important TEMs which would have been informative to include in the population-adjusted ITCs.

Issue 2: MAICs reflect a 'RATIFY-like' population which is not representative of current NHS clinical practice

A major limitation of the MAICs is exclusion of 38.6% of the QuANTUM-First ITT population aged between 60 and 75 years at baseline, in order to match TEMs to a 'RATIFY-like' population which, by the inclusion criteria of the RATIFY trial was restricted to <60 years. Clinical advice to both the company and the EAG is that the QuANTUM-First ITT population is more representative than the RATIFY trial population of the NHS population who would be eligible for treatment with quizartinib. The relative effect estimates calculated using MAIC which have been estimated within a 'RATIFY-like' population cannot be transposed to different populations. Therefore, the EAG considers that the results of the MAICs are not applicable to an NHS population who would be eligible for treatment with quizartinib and are not suitable for decision making.

Issue 3: Bias in ITCs of CIR following CR due to adjustment of non-randomised groups

The company identified TEMs for OS only from their literature review, as subgroup analyses for OS only were presented in publications of the RATIFY trial and not for CR or CIR following CR. Clinical advice to both company (response to clarification question A12) and to the EAG indicated that it is reasonable to assume that TEMs for OS would be the same for CR and CIR following CR.

OS and CR were analysed within the ITT population (i.e., all randomised patients) and therefore it is expected/likely that any TEM characteristics will be balanced across the treatment groups due to

randomisation. The absence of evidence to separately identify TEMs for CR, the EAG considers it is reasonable to assume that TEMs are the same for OS and CR.

CIR, however, is analysed within the subset of randomised patients who achieved CR, and therefore randomisation is broken between baseline and the time of achieving CR, and the probability of achieving CR is related to the treatment received (i.e. quizartinib or placebo [plus standard chemotherapy]). Therefore, any imbalances in patient characteristics within the non-randomised treatment groups of the QuANTUM-First trial are likely to impact upon the matching process and the reweighting of patient characteristics identified as TEMs. The EAG also considers that it is not appropriate to match characteristics of those who have achieved CR (in the QuANTUM-First trial) to the baseline characteristics of all patients within the *FLT3-ITD*+ subgroup of the RATIFY trial.

As acknowledged by the company, four patients in the placebo + standard chemotherapy group of QuANTUM-First trial with higher weights due to an imbalance in platelet counts between the trials after weighting seem to have influenced the matched outcomes for the MAIC of CIR. The EAG notes that the difference between the CIR rate in the unadjusted and adjusted placebo arms is substantial (CS, Figure 18) and such a large difference is not present for OS, despite inclusion of the same patients (CS, Figure 17).

Also as acknowledged by the company, the estimated incidence of relapse curves from the ML-NMR of CIR are not a good fit to KM curves from the QuANTUM-First study, indicating likely bias in the ML-NMR results for CIR. This bias may be due to low patient numbers and differences in prognostic factors as suggested by the company.

It should also be noted that the results of naïve comparisons of the QuANTUM-First and RATIFY studies for CIR do not align with the results of the MAIC (Table 9) or the ML-NMR (Table 12), suggesting less of a numerical advantage for quizartinib over midostaurin, and no statistically significant evidence of a difference between the treatments.

The EAG considers that adjustment of covariates which are likely imbalanced in the non-randomised groups achieving CR in the QuANTUM-First trial, and adjustment for aggregate level covariates of all *FLT3-ITD*+ patients at baseline from the RATIFY trial (CS, Appendix M, Table 3), rather than patients who achieved CR may have also contributed to the biases in the MAICs and ML-NMRs of CIR. The EAG considers that this issue is unresolvable using population-adjusted ITC methods.

Issue 4: Incorrect application of population-adjusted ITC results within economic modelling
An important difference between the company MAIC and ML-NMR approaches is the target estimands (i.e. the quantity estimated within the statistical analysis, CS, Appendix M, Section 1.3) that each approach produces and the interpretation of these estimands)[51, 55].

The company MAICs, and MAICs generally, estimate the population-average *marginal* treatment effect, i.e. the difference between the population who have all received quizartinib versus the difference between the population who have all received midostaurin. Marginal treatment effects are commonly the estimand of interest for NICE decision making. In other words, the marginal treatment effect in this context represents the effect of moving everyone within the target population (regardless of their observed characteristics) from treatment with midostaurin to treatment with quizartinib. Marginal treatment effects depend upon the distribution of all prognostic and TEM covariates and the distribution of baseline hazard in the target population. Constant (i.e. non-time varying) marginal HRs additionally depend on the length of follow-up and the censoring distribution[56].

Whereas the estimand generated within the company ML-NMR is the population-average *conditional* treatment effect, which has a different interpretation to the marginal treatment effect. Population-average conditional treatment effects are interpreted as the average of the individual treatment effects in the population, i.e. the average effect of moving each individual within the target population from treatment with midostaurin to treatment with quizartinib. ML-NMR produces population-average conditional estimates by averaging predictions on the linear predictor scale over the target population, which simplifies to a linear combination of coefficients of the regression model and mean TEM characteristics in the target population [51]. Therefore, a population-average conditional treatment effect depends only upon the average TEM covariate values within the target population, and not on the distribution of prognostic factors or baseline hazard.

HRs and ORs are non-collapsible measures, which means that conditional and marginal treatment effect estimates may not align, even where covariates are balanced [55]. Conditional effect measures are specific to a target population with a given distribution of TEM characteristics. Marginal effect measures are specific to a target population with given distributions of prognostic and TEM characteristics and baseline hazard. Crucially, the different interpretation of population-average conditional and marginal effects means that they must be applied appropriately for economic modelling.

The company approach of applying a conditional HR to a baseline KM curve which is unadjusted for the covariates of interest (see Section 4.2.6.2), will result in bias which is similar to aggregation bias which is recognised to be associated with some forms of the population-adjustment approach simulated treatment comparison [53, 55]. In other words, directly applying a population-average conditional OS effect estimate for quizartinib versus midostaurin to unadjusted individual level survival data for quizartinib will result in biased survival estimates for midostaurin, due to the non-linearity of the survival model and non-collapsibility of HRs.

It should be noted that marginal treatment effects can be estimated via ML-NMR (see Section 2.5 of Phillippo *et al.* [53]), which could be applied to an unadjusted baseline KM curve. However, the use of population-adjusted ITC methods (i.e. MAIC or ML-NMR) is motivated by the existence of covariate effects. However, when covariate effects are present (prognostic or effect-modifying), hazards are mathematically non-proportional at a marginal level [53, 56]. Therefore, the company approach of only fitting models which assume PH within their population-adjusted ITCs, summarising relative effects (whether conditional or marginal) using constant HRs and applying these constant HRs to baseline survival curves in an economic model is inappropriate and contradicts the assumed existence of covariate effects. The EAG considers that the constant HRs from both the MAICs and the ML-NMRs are unsuitable for decision making.

A correct approach to cost-effectiveness analysis assuming the existence of covariate effects, would be to use the average survival curves for each treatment in the target population predicted within the ML-NMR (i.e. those presented in CS, Appendix M, Figure 1, and Figure 3) directly within the economic model rather than applying conditional (constant) HRs to unadjusted baseline KM data, extrapolated using parametric survival modelling.

3.5.2 Quizartinib vs. sorafenib (post-HSCT maintenance therapy)

The company ITC to compare the efficacy of quizartinib and sorafenib post-HSCT maintenance therapies is presented in response to clarification question A9. An unanchored MAIC for OS was conducted using IPD from the QuANTUM-First trial, and digitised KM data from the SORMAIN trial. The results of the unanchored MAIC were used to inform a scenario analysis for the company's economic model (response to clarification question B9).

3.5.2.1 Selection of treatment effect modifiers and prognostic factors

In line with TSD 18[49], in additional to matching for TEMs, unanchored MAICs additionally match for prognostic variables. The company included the same four TEMs which were included in the MAICs of quizartinib vs midostaurin (age, sex, platelet count and *NPM1* mutation) and also included WBC as a TEM, as summary data were available for this characteristic from the SORMAIN trial. The company also included cytogenic risk score and ECOG performance score (PS) as prognostic variables. Where values may have changed during the QuANTUM-First trial, variables measured at the beginning of maintenance were used in the matching process (i.e., age platelet count. WBC, ECOG PS; Table 3, response to clarification question A9).

3.5.2.2 Unanchored MAIC methods

The company undertake an unanchored MAIC as the quizartinib and placebo arms of the QuANTUM-First trial can no longer be treated as randomised groups at the start of maintenance therapy. Although patients were randomised to quizartinib or placebo (plus standard chemotherapy

during induction and consolidation phases), the treatments received during these phases are related to the probability of a patient entering the maintenance phase and therefore randomisation is broken between the start of treatment and the start of maintenance phase, so the common placebo arm in the two trials cannot be used as an anchor. Instead, the quizartinib arm (including patients who received post-HSCT maintenance therapy) was matched directly to the sorafenib arm of the SORMAIN trial.

The company unanchored MAIC followed the same general process with regards to matching of TEMs and prognostic variables and calculation of a HR and 95% CI for OS (see Section 3.5.1.2).

The company also performed naïve comparisons of quizartinib vs sorafenib post-HSCT maintenance therapy to serve as a reference to the unanchored MAIC.

3.5.2.3 Unanchored MAIC results

A summary of the patient baseline characteristics of the adjusted quizartinib post-HSCT maintenance group following reweighting of age, sex, *NPM1* mutation status, platelet count, WBC, cytogenic risk and ECOG PS is provided in Table 4 of the response to clarification question A9. The ESS of the quizartinib post-HSCT maintenance group reduced to [redacted]. Following reweighting, minor imbalances remained between the trial populations in median platelet count and WBC count, and *NPM1* mutation status.

Results of the unanchored MAICs (and the naïve comparison as a reference) are reported in Table 11.

Table 11 Unanchored MAIC and naïve comparison of quizartinib and sorafenib post-HSCT maintenance therapy for OS

Analysis	Comparison	OS HR (95% CI)*
Naïve comparison	Quizartinib vs. Sorafenib	[redacted]
Unanchored MAIC	Quizartinib vs. Sorafenib	[redacted]

***** HR<1 favours the first treatment over the second treatment in the comparison.

Source: Response to clarification question A9, Table 6

The unanchored MAIC showed a [redacted] for sorafenib post-HSCT maintenance therapy compared to quizartinib post-HSCT maintenance therapy [redacted] for OS (HR [redacted], 95% CI: [redacted]). The naïve comparisons for OS provided very similar results (HR [redacted], 95% CI: [redacted]).

3.5.2.4 EAG comments

The EAG considers that the company seem to have correctly implemented the unanchored MAICs, with adequate population overlap as demonstrated by the ESS and few outliers with high weights (Figure 1, response to clarification question A9).

Issue 1: Limited and uncertain evidence available for the comparison of quizartinib and sorafenib post-HSCT maintenance therapy for decision making

The EAG acknowledges the company reasoning for performing an unanchored MAIC of OS for quizartinib and sorafenib post-HSCT maintenance therapy. However, the EAG considers that there is inherent uncertainty associated with unanchored MAICs, due to the strong assumption that all TEMs and prognostic factors are included and adjusted for, an assumption which is difficult to assess[49] and is unlikely to be met in this context due to lack of comparable available data on some baseline characteristics across the trials.

While associated with limitations, the EAG suggests than an anchored MAIC of the QuANTUM-First and SORMAIN trials, supported by a naïve comparison as a reference, may have been feasible by first adjusting the baseline characteristics of the quizartinib and placebo post-HSCT maintenance groups in the QuANTUM-First trials for imbalances, e.g. using propensity score matching or covariate adjustment methods.

The EAG emphasises potential limitations of the constant HR estimated for the OS comparison of quizartinib and sorafenib post-HSCT maintenance therapy (see Issue 4 in Section 3.5.1.6 for further discussion). The validity of the PH assumption in this ITC of OS is unknown and cannot be assumed to hold in the presence of covariate effects. However, the similarity of the results of the unanchored MAIC and naïve comparison suggests that any differences in patient characteristics between the quizartinib post-HSCT maintenance group of the QuANTUM-First trial and the sorafenib group of the SORMAIN trial have not had any meaningful impact on the results of the ITC. Comparison of the results of an anchored MAIC and a naïve comparison of the QuANTUM-First post-HSCT maintenance and the SOMAIN trial population would also further inform the existence and impact of any population differences and covariate effects.

The EAG also notes that no evidence is provided for comparative effect of quizartinib and sorafenib post-HSCT maintenance therapy in terms of relapse. The company ITCs of quizartinib versus midostaurin compared CIR following CR as a proxy of RFS, as RFS was not collected in the RATIFY trial (CS, p84) and the CIR ITC results are used as a proxy for RFS in the economic model (CS, p217). The QuANTUM-First and SORMAIN trials both report RFS data and therefore, the EAG considers that an ITC of RFS comparing quizartinib and maintenance therapy post-HSCT should have been feasible and could have been used within the scenario analysis for the company economic model (response to clarification question B9).

3.6 Additional work on clinical effectiveness undertaken by the EAG

As reference to the ML-NMR results and to provide additional supportive evidence to inform the comparisons between quizartinib and midostaurin, the EAG performed two additional naïve, unadjusted indirect comparisons.

3.6.1.1 Naïve comparison between QuANTUM-First and RATIFY FLT3-ITD+ population

To serve as a reference to the company ML-NMR results, the EAG performed naïve, unadjusted comparisons using OS, CR and CIR data from the QuANTUM-First ITT population and RATIFY *FLT3-ITD*+ population (Table 12).

Table 12 Company ML-NMR results and EAG naïve comparison of QuANTUM-First ITT population and RATIFY *FLT3-ITD* population: results for OS, CR and CIR

Analysis	Comparison	OS	CR	CIR
		HR (95% CI)[a]	OR (95% CI)[b]	HR (95% CI)[a]
QuANTUM-First ITT population	Quizartinib vs. placebo	0.78 (0.62 to 0.98)	0.98 (0.70 to 1.37)	0.62 (0.43 to 0.90)
RATIFY *FLT3-ITD*+ subgroup	Midostaurin vs. Placebo	0.79 (0.59 to 1.06)	1.25 (0.79 to 1.99)	0.80 (0.56 to 1.15)
Company ML-NMR results	Quizartinib vs. Midostaurin	1.02 (0.67 to 1.56)	0.63 (0.34 to 1.19)	0.49 (0.23 to 1.00)
EAG naïve comparison	Quizartinib vs. Midostaurin	0.99 (0.68 to 1.43)	0.78 (0.44 to 1.39)	0.61 (0.31 to 1.20)

[a] HR<1 favours the first treatment over the second treatment in the comparison.
[b] OR>1 favours the first treatment over the second treatment in the comparison.
Abbreviations: CI: confidence interval; CIR: cumulative incidence of relapse; CR: complete remission; *FLT3-ITD*: FMS-like tyrosine kinase 3 internal tandem duplication; ITT: intention to treat; HR: hazard ratio; ML-NMR: multilevel network meta-regression; OR: odds ratio; OS: overall survival

Naïve comparisons for OS and CR provided numerically similar results to the company ML-NMR results. For CIR, the numerical advantage for quizartinib over midostaurin was smaller and no longer statistically significant in the naïve comparison compared to the ML-NMR results, suggesting that adjustments applied within the ML-NMR favour quizartinib over midostaurin.

3.6.1.2 Naïve comparison using AMLSG 16-10 trial of midostaurin

The EAG has noted several important limitations of the available evidence from the *FLT3-ITD*+ subgroup of the RATIFY trial including the restriction to patients aged < 60 years, lack of CRc outcome data and lack of data for several relevant treatment effect modifiers (see Section 3.4.1.1).

As additional supportive evidence to address some of these limitations and further explore uncertainty, the EAG requested that the company perform an unanchored MAIC of quizartinib and midostaurin using OS, CRc and CIR data from the quizartinib arm of the QuANTUM-First trial and the midostaurin arm of the AMLSG 16-10 trial[34](clarification question A17).

In response to clarification question A17, the company performed a feasibility assessment of conducting ITCs of OS, CRc and CIR using data from the QuANTUM-First and AMLSG 16-10 trials. Trial characteristics and patient baseline characteristics of the QuANTUM-First and AMLSG 16-10 trial are presented in Table 14 and Table 15 of the response to clarification question A17. The company noted the following differences between the QuANTUM-First and AMLSG 16-10 trials:

- Eligibility criteria for age were 18 to 75 years in the QuANTUM-First trial versus 18 to 70 years in the AMLSG 16-10 trial, however the EAG notes that median age was similar across the two trials (56 years in the QuANTUM-First trial compared to 54.1 years in the AMLSG 16-10 trial).
- The AMLSG 16-10 trial was a non-randomised, open label, single arm trial of midostaurin (plus standard chemotherapy) with comparison made to a historical cohort of patients treated with standard chemotherapy without midostaurin from five prior AMLSG trials whereas the QuANTUM-First trial was a double-blinded comparison of quizartinib and placebo (plus standard chemotherapy).

The company also notes some slight differences in baseline characteristics between the trials (Table 15 of the response to clarification question A17).

The company conclude that despite their feasibility assessment indicating that a MAIC of quizartinib and midostaurin using the QuANTUM-First and AMLSG 16-10 trials is 'likely technically possible' (response to clarification question A17), due to significant limitations from the restricted evidence base to match for all relevant TEMs and prognostic factors, a strong assumption associated with unanchored MAICs (see Section 3.5.2.4), results of an unanchored MAIC are expected to be associated with bias and that an unanchored MAIC using data from the QuANTUM-First and AMLSG 16-10 trials would not provide evidence which is 'more reliable or robust' than the population-adjusted ITCs of the QuANTUM-First and RATIFY trials.

The EAG agrees with the company regarding the inherent uncertainty associated with unanchored MAICs due to the strong assumptions associated with them. However, the EAG notes that aside from the differences in trial design mentioned by the company, the patient populations and characteristics, trial procedures and outcome definitions of the QuANTUM-First and AMLSG 16-10 trials are quite similar, and arguably the QuANTUM-First and AMLSG 16-10 trials are more comparable than the QuANTUM-First and RATIFY trials.

Therefore, the EAG still considers that an ITC of the QuANTUM-First and AMLSG 16-10 trials would provide useful additional supportive evidence to address some of the limitations of the company's ITC. In the absence of IPD from either trial to attempt any matching, the EAG can only perform naïve comparisons. EAGs naïve comparisons assume that the historical control group used

the AMLSG 16-10 trial (consisting of patients from the standard chemotherapy groups of five previous AMLSG trials) and the placebo group of the QuANTUM-First trial are a common control group to anchor the comparison. It should be noted that there may be important differences in between these control groups, particularly relating to the time frame of the historical control group of the AMLSG 16-10 trial who were enrolled into trials between 1993 and 2009, compared to the placebo group of the QuANTUM-First trial who were enrolled between 2016 and 2019.

Furthermore, available published data for CIR varies for the two trials. Both trials report CIR following CRc, however, neither report an unadjusted HR and 95% CI. The EAG has digitised cumulative incidence data from Figure S7 of Erba et al[28] publication of the QuANTUM-First trial and estimated a HR and 95% CI for CIR following CRc. It should be noted that it is not possible to distinguish between competing events of relapse and death from digitised data to align with the competing risks analysis of CIR following CRc in the QuANTUM-First trial. Published cumulative incidence data for CIR following CRc is available for only a limited time frame of up to 8 months (Supplementary Figure 3 of Döhner et al [34]), and the only comparative effect estimate for CIR following CRc available is an adjusted HR and 95% CI from a multivariate analysis including cohort (i.e. AMLSG 16-10 midostaurin cohort or historical cohort) as a covariate, and also adjusting for age, sex, NPM1 mutation, WBC, bone marrow blasts, FLT3-ITD subtype (high or low) (Supplementary Table 10 of Döhner et al [34]).

Results of EAG naïve comparisons of QuANTUM-First and AMLSG 16-10 trials for OS, CR, CRc and CIR following CRc are presented in Table 13. Due to the limitations described above with the EAG naïve comparisons using published data only, all results should be treated as exploratory, particularly results for CIR following CRc.

Table 13 EAG naïve comparison of QuANTUM-First trial (ITT population) and AMLSG 16-10 trial (midostaurin cohort and historical control cohort): results for OS, CR, CRc and CIR

Analysis	Comparison	OS	CR	CRc	CIR[c]
		HR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[b]	HR (95% CI)[a]
QuANTUM-First ITT population	Quizartinib vs. placebo	0.78 (0.62 to 0.98)	0.98 (0.70 to 1.37)	1.10 (0.85 to 1.44)	0.64 (0.45 to 0.91)[c]
AMLSG 16-10 trial FAS	Midostaurin vs. Historical controls	0.56 (0.47 to 0.68)	0.75 (0.59 to 0.96)	1.16 (0.94 to 1.43)	0.37 (0.29 to 0.48)[c]
Naïve comparison	Quizartinib vs. Midostaurin	1.39 (1.03 to 1.88)	1.31 (0.86 to 1.98)	0.95 (0.67 to 1.33)	1.32 (0.71 to 2.46)

[a] HR<1 favours the first treatment over the second treatment in the comparison.
[b] OR>1 favours the first treatment over the second treatment in the comparison.
[c] Data are extracted for CIR from time of CRc for both studies. HR and 95% CI calculated from digitised cumulative incidence data from Figure S7 of Erba *et al*[28] publication of the QuANTUM-First trial and adjusted HR and 95% CI from a multivariate analysis also including cohort (i.e. AMLSG 16-10 midostaurin cohort or historical cohort), age, sex, *NPM1* mutation, WBC, bone marrow blasts, *FLT3-ITD* subtype (high or low) from Supplementary Table 10 of Döhner et al [34].

Abbreviations: CI: confidence interval; CIR: cumulative incidence of relapse; CR: complete remission; CRc: complete composite remission; FAS: full analysis set; *FLT3-ITD*: FMS-like tyrosine kinase 3 internal tandem duplication; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intention to treat; KM: Kaplan-Meier; *NPM1*: nucleophosmin gene; OR: odds ratio; WBC: white blood count

EAG naïve comparisons show a statistically significant advantage for midostaurin over quizartinib (HR 1.39, 95% CI: 1.03 to 1.88), a numerical advantage to quizartinib over midostaurin for CR which is not statistically significant (OR 1.31, 95% CI: 0.86 and 1.98) and a numerical advantage for midostaurin over quizartinib for CIR following CRc which is not statistically significant (HR 1.32; 95% CI: 0.71 and 2.46).

The EAG naïve comparisons provide the only evidence regarding the comparative effect of quizartinib and midostaurin in terms of CRc and suggest no difference between the treatments (OR 0.95, 95% CI: 0.67 to 1.33).

Overall, while associated with significant limitations, the EAG naïve comparisons QuANTUM-First and AMLSG 16-10 trials suggest different directions and variable magnitude of effect of the comparative efficacy of quizartinib and midostaurin compared to the company ITCs of the QuANTUM-First and RATIFY trials (Section 3.5.1.4 and 3.5.1.5) which raises uncertainty regarding the relative efficacy of quizartinib compared to midostaurin.

The EAG emphasises the exploratory nature of these naïve comparisons and considers that a population-adjusted ITC using IPD from the QuANTUM-First trial matched with published data from the AMLSG 16-10 trial, despite inherent limitations, would likely be more robust and informative to further explore uncertainties in the comparative effects of quizartinib and midostaurin.

3.7 Conclusions of the clinical effectiveness section

The evidence presented in the CS on the efficacy and safety of quizartinib for untreated FLT3+-ITD AML is primarily based on the results of the QuANTUM-First trial, which evaluated quizartinib in combination with standard induction and consolidation chemotherapy and then continued as monotherapy for up to 36 cycles compared with placebo. Results presented from an August 2021 data cut-off showed improved OS overall in the quizartinib arm compared to the placebo arm, but subgroup analyses showed potential evidence of heterogeneity by age, sex, WBC count, *NPM1* mutation status, and in the maintenance setting, by prior use of HSCT. Improved RFS, higher rates of CRc and lower rates of CIR were observed in the quizartinib arm compared to the placebo arm. Differences between treatment arms varied by the definition of EFS. CR rates and transplant rates were similar between the treatment arms, and there was no difference between treatment arms in HRQoL. Quizartinib leads to higher rates of AEs, TEAEs (including neutropenia), SAEs, early deaths at 30 to 60 days from treatment initiation, and discontinuations/dose adjustments of study drug due to AEs compared to placebo. Cardiac deaths were reported in the quizartinib arm and the cardiac risk of

quizartinib is uncertain based on the evidence presented. The tolerability of quizartinib is notably more limited in the maintenance phase, and most patients did not complete the full maintenance course of 36 cycles.

The results of the QuANTUM-First trial are subject to limitations. Firstly, the PH assumption was violated within analyses of OS, EFS and RFS and therefore the constant HRs estimates will not be reflective of the relative efficacy of quizartinib compared to placebo at all time points. Secondly, the QUANTUM-First trial was not designed to estimate the efficacy and safety of separate phases of quizartinib therapy, therefore important clinical benefits and harms cannot be isolated by treatment phase and the relative efficacy and safety of quizartinib and placebo in the consolidation, maintenance and long-term follow-up phases is uncertain and may be confounded by the efficacy and safety of treatment received in prior phases.

Evidence presented in the CS appropriately limited the choice of comparators to midostaurin, considering all treatment phases. In the absence of head-to-head evidence comparing quizartinib and midostaurin, the company conducted population adjusted ITCs (MAICs and ML-NMRs) of OS, CR and CIR including the QuANTUM-First trial and the *FLT3-ITD+* subgroup of the RATIFY trial.

The EAG considers that the company have not provided robust evidence of any efficacy or safety advantage for quizartinib over midostaurin. Differences in trial design and outcome data between the QuANTUM-First and RATIFY trials impact upon the interpretation of the ITCs results and their generalisability to NHS clinical practice. Relative effect estimates calculated using MAICs, used within the company base case for their economic model, have been estimated within the RATIFY *FLT3-ITD+* subgroup, which is not reflective of the target population for decision making. Results of ML-NMRs reflect the QuANTUM-First ITT population, a population which is representative of the target population who would be treated with quizartinib in the NHS. However, the company approach of fitting ML-NMR models which require the PH assumption and applying the estimated constant HRs to baseline survival curves contradicts the assumed existence of covariate effects. Therefore, both MAICs and ML-NMRs population-adjusted ITCs are unsuitable for decision making.

In addition, sorafenib is a commonly used, off-licence and off-patent treatment recommended by NHS England in the post-HSCT maintenance setting but is not a comparator in the company's decision problem nor in the company's base case. An unanchored MAIC of OS, supported by a naïve comparison performed by the company at clarification, shows no evidence that quizartinib was superior to sorafenib in a post-HSCT maintenance setting. However, unanchored MAIC results are uncertain and subject to a number of significant limitations. No comparative evidence for other relative efficacy and safety outcomes is available for quizartinib compared to sorafenib in a post-HSCT maintenance setting.

4 COST EFFECTIVENESS

4.1 Critique of the company's review of cost-effectiveness evidence

The company undertook a SLR to identify relevant economic evaluations of adult patients with *FLT3*+ AML.

4.1.1 Search strategy

The CS included the searches to identify studies on the cost-effectiveness of interventions for *FLT3*+ AML in Appendix G.

The EAG found that the searches were generally appropriate and of a good standard. However, the original searches in the November 2023 company submission were not updated for the March 2024 or the April 2024 company submissions. Therefore, more recent economic evaluations would not have been identified by the searches presented. The EAG appraisal of the searches can be found in Appendix Table 40.

4.1.2 Inclusion/exclusion criteria

Study eligibility criteria applied by the company were described in CS, Appendix G for the review of economic evaluations. Non-English language studies were excluded. A date limit was also applied. Full papers published pre-2012 were excluded, as were conference abstracts pre-2020. The characteristics of the population considered in the review of economic evaluations was broadly similar to that considered in QuANTUM-First trial (Section 3.2.2) At both the title/abstract review phase and the full publication review phase, studies were reviewed by two independent reviewers with discrepancies referred to a third analyst, where these were resolved by consensus.

The EAG considered the eligibility criteria and the company's assessment of identified studies against them to be appropriate.

4.1.3 Identified studies

The review of economic evaluations identified a total of 8 relevant studies for inclusion (CS, Appendix G, Table 6). These included 3 studies considering a UK NHS setting (CS, Document B, Table 42). The identified studies include two HTA submissions: TA523 midostaurin for untreated acute myeloid leukaemia[21] and TA642 gilteritinib for treating relapsed or refractory acute myeloid leukaemia.[57]

4.1.4 Interpretation of the review

The EAG considered the methods of the company's SLR sufficient to identify any existing cost-effectiveness analyses conducted in a relevant population and setting. As no relevant economic evaluations of quizartinib were identified by the review, the EAG is satisfied that the model presented by the company represents the most relevant analysis for decision-making.

4.2 Summary and EAG critique of the company's submitted model structure and model parameters

4.2.1 NICE reference case checklist

Table 14 summarises the EAG's assessment of whether the company's economic evaluation meets the NICE reference case and other methodological recommendations.

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALY benefits for treated individuals were accounted for
Perspective on costs	NHS and PSS	An NHS and PSS perspective on costs was considered
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	A cost-utility analysis was implemented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model adopted a 53-year (lifetime) time horizon. This suitably captured lifetime costs and benefits.
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review to identify relevant data sources. The company undertook an MAIC and ML-NMR of available trial evidence to inform relative effectiveness estimates.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs. Modelled health state utilities were based on multiple published sources. Utility values for the induction and CR 1L health state were based on EQ-5D-3L observed in patients with AML. Utility values applied to the consolidation and maintenance phase were based on TTO values, elicited from the general public. Health states described in the TTO exercise were for MDS, not AML. Utility values for the refractory, relapse 1L and HSCT 1L health states were based on QLQ-C30 values mapped to EQ-5D.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	

Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs based on UK sources including eMIT, NIHR (iCT), BNF and NHS reference costs. Resource use based on previous appraisals and clinical advice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5% per annum

Abbreviations: 1L: first line; AML: acute myeloid leukaemia; BMF: British National Formulary; CR: complete remission; eMIT: electronic market information tool; EQ-5D: standardised instrument for use as a measure of health outcome; HSCT: allogeneic haematopoietic stem cell transplantation: MAIC; matching adjusted indirect treatment comparison; MDS: myelodysplastic syndrome; ML-NMR: multilevel network meta-regression; NIHR iCT: National Institute for Health and Care Research interactive costing tool; PSS, personal social services; QALYs: quality-adjusted life years; QLQ-C30: Core Quality of Life questionnaire; TTO: time on treatment

4.2.2 Model structure

The company developed a Markov state transition model (STM) in Microsoft Excel to simulate the lifetime cost-effectiveness of quizartinib for the treatment of patients newly diagnosed with *FLT3-ITD*+ AML. The economic analysis compares a quizartinib based treatment regimen with established clinical management consisting of either a midostaurin based treatment regimen or standard chemotherapy (SC). The model uses a 28-day cycle length with half-cycle correction applied. The model structure integrates first-line (1L) and second-line (2L) treatment, encompassing ten 'alive' health states. In 1L, the modelled health states are: Induction, CR 1L, Refractory (1L), Relapse (1L), HSCT (1L), and Post-HSCT relapse 1L. In 2L the modelled health states are: Complete remission in 2L (CR2 L), Relapse 2L, HSCT 2L, and Post-HSCT maintenance 2L. In addition to the 'alive' health states, an absorbing death health state was modelled. The model structure and transitions are depicted in Figure 7. The health states are described in Table 15.

The model was developed to allow the modelling of 'functional cure' in patients experiencing long-term remission. Patients who remain in the CR 1L and HSCT 1L health states at cycle 40 of the model (approx. 3 years) are assumed to be functionally cured. Patients who are functionally cured are no longer at risk of relapse or mortality due to AML. However, longer-term excess mortality due to other causes (e.g. higher risk of secondary cancers, cardiac events, etc.) is assumed for the remainder of the model time horizon by applying a standard mortality ratio (SMR) of 2 to general population mortality rates. Following the cure point, patients are assumed not to incur disease management costs, and their utilities were assumed to be the same as those of the general population adjusted for age and sex.

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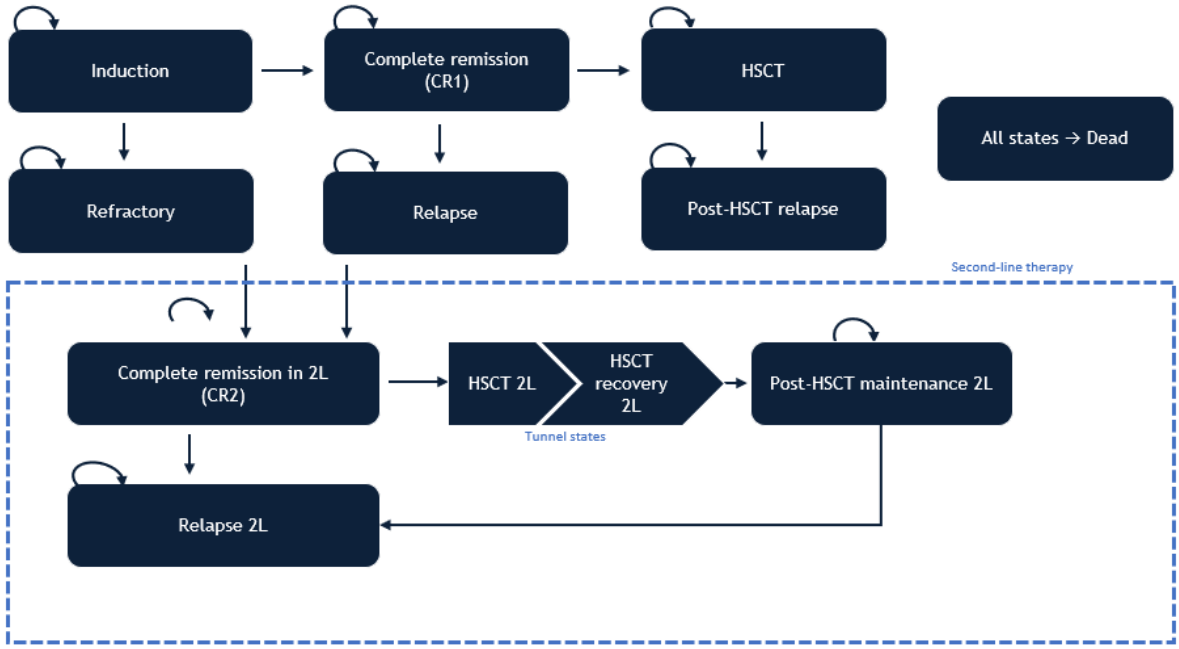
Figure 7 Model Schematic (adapted from from CS, Figure 21)



Abbreviations: HSCT: allogeneic haematopoietic stem cell transplantation; CR: complete remission; CR1: first CR; CR2: second CR first-line treatment; 2L: second-line treatment.

Table 15 Model health states (adapted from Table 43 of the CS)

Health state	Description
Induction	• Initial period of treatment with quizartinib, midostaurin or SC alone prior to determination of response status • Duration: Comprises of two sub-tunnel states Induction 1 and Induction 2 representing 1 and 2nd induction.
CR 1L	• Patients who attain CRc in the induction phase enter this state and can receive consolidation therapy for up to 4 cycles. Those who complete consolidation treatment continue to maintenance treatment, which lasts up to 36 cycles for the quizartinib regimen, and up to 12 cycles for the midostaurin regimen. • Duration: Patients remain in this health state until they experience relapse or death or have an HSCT. Patients remaining in this health state at cycle 40 (approx. 3 years) become 'functionally cured.'
Refractory (1L)	• Refractory patients (those who failed induction therapy). Patients receive salvage therapy consisting of either gilteritinib or high-intensity chemotherapy. • Duration: Patients remain in this health state until they either achieve remission (CR 2L) or die.
Relapse 1L	• Patients who subsequently relapse following CR 1L. Patients receive salvage therapy consisting of either gilteritinib or high-intensity chemotherapy. • Duration: Patients remain in this health state until they either achieve remission (CR 2L) or die.
HSCT 1L	• Period of HSCT procedure and recovery. Patients enter from CR 1L health state. • Duration: Patients remain in this health state until they experience relapse or death. Patients remaining in this health state at cycle 40 (approx. 3 years) become 'functionally cured.'

Post-HSCT relapse 1L	• Patients who subsequently relapse following HSCT 1L. Patients receive salvage therapy consisting of either gilteritinib or high-intensity chemotherapy. • Duration: Patients are assumed to remain in the 'post-HSCT relapse' state until they die.
CR 2L	• Patients who relapse following 1L therapy may achieve a 2L remission. • Duration: patients remain in this health state until they experience relapse or death or have an HSCT. Unlike CR 1L, patients remaining in this health state do not become 'functionally cured' at cycle 40 (approx. 3 years).
Relapse 2L	• Patients who subsequently relapse following CR 2L or HSCT 2L • Duration: Patients remain in this health state until they die.
HSCT 2L and HSCT recovery	• Period of HSCT procedure and recovery. Patients enter from CR 2L health state. • Duration: Patients remain in this health state for 13 cycles transitioning through 13 tunnel states before transitioning to the Post-HSCT maintenance 2L. The 13 tunnel states comprise of three HSCT cycles, representing the transplantation phase without treatment, and ten HSCT recovery cycles, where maintenance treatment may commence.
Post-HSCT maintenance 2L	• Period after HSCT 2L recovery. • Duration: patients remain in this health state until they experience relapse or death. Unlike HSCT 1L, patients do not become 'functionally cured' at cycle 40 (approx. 3 years).
Dead	• Dead

Abbreviations: HSCT: allogeneic haematopoietic stem cell transplantation; CR: complete remission; CRc: composite complete remission; 1L: first-line treatment; 2L: second-line treatment.

EAG comments

Modelling approach

The company has opted to develop an STM instead of a partition survival model (PSM), a method commonly used in economic evaluations of advanced cancer treatments. An STM is a more complex approach and is more challenging to critique due to the difficulties in determining the flow of patients through the model. The STM determines state occupancy based on explicitly modelled transitions which define the structural links between health states, differences in survival outcomes are determined by the combined effect of each treatment on individual transition probabilities and the structural relationships assumed between health states. The EAG discusses several important consequences of the STM modelling approach below.

i) Concerns raised in TA523

In TA523, a PSM was chosen due to its straightforward implementation with available patient-level data and its alignment with trial data; health state occupancy was determined based on the area under the curves fitted to trial outcomes. However, patients who did not respond or relapsed after 1L therapy were moved to the relapsed health state, where they could not achieve CR and could only transition to HSCT or death. This failed to account for the benefit of 2L treatment, assuming all patients in the

relapse state had the same QoL and costs. This limitation was a major point of criticism by the EAG in TA523, leading to an underestimation of the incremental cost-effectiveness ratio (ICER). A significant advantage of the STM approach is that it allows for a more nuanced modelling of 2L treatment, directly addressing concerns raised in TA523. The EAG also considers this an important advantage in the context of the current decision problem, given the recent approval of gilteritinib, see point ii below for further discussion.

ii) Modelling 2L treatment

A significant limitation of the QuANTUM-First and RATIFY trials is that they do not reflect currently available 2nd line therapy. Current NHS practice for relapsed or refractory *FLT3*+ AML recommends gilteritinib which was approved as 2nd line therapy in NICE TA642. Gilteritinib was not widely available when the QuANTUM-First or RATIFY trials were conducted. Consequently, the OS data do not capture the survival advantage provided by gilteritinib. The STM approach allows evidence on the effectiveness of gilteritinib to be incorporated into the model, even in the absence of OS data directly from the QuANTUM-First and RATIFY trials. This is a potentially important advantage (relative to a PSM) as one of the primary claimed benefits of quizartinib relative to both midostaurin and SC is that it reduces the risk of relapse. Accurately reflecting the consequences of relapse (both in terms of costs and QALYs) is therefore important.

iii) Surrogate relationship between OS and relapsed/refractory disease

An important consequence of the STM approach is that OS as observed in the trial data is not directly used in the economic analysis, instead, OS is determined by structural links inherent to the adopted model structure. In the company's base model, the rates of remission, relapse, and refractory disease, as well as the proportion of patients receiving HSCT, determine OS. The model therefore effectively implies structural surrogate relationships between these intermediate outcomes and OS. In this context, the EAG views the STM approach and implied surrogate relationships to be reasonable but notes that deriving survival OS from surrogate endpoints instead of inferring them directly from the trial can compromise the accuracy of the model's predictions, especially if the relationships between the surrogates and OS are unclear or data informing surrogate outcomes does not represent a subset of the original trial data.

On this point, the EAG highlights that model predictions for OS do not align with the observed QuANTUM-First trial even when the model is calibrated to use unadjusted QuANTUM-First population and KM data from the trial. The company’s response to clarification question B2 provided limited reassurance or explanation for this divergence summarising that this expected as adjusted OS is not directly used in the model. The EAG would like to see a more comprehensive response than the

one provided, and it remains unclear why there is such a divergence between the model and the observed data (response to clarification question B2, Table 29).

The assumed surrogate relationships are also important in interpreting the evidence from the ITC. The economic model predicts substantive life years gained (LYG) for quizartinib relative to midostaurin driven primarily by the treatment effect applied to relapse from CRc. This, however, contradicts results from both the company's MAIC and ML-NMR of OS (see Section 3.5.1.3 and Section 3.5.1.5) which show no evidence of survival benefit in favour of quizartinib. Indeed, results using the AMLSG 16-10 trial[34] suggest that midostaurin may be superior to quizartinib. While the EAG acknowledges the limitations of these indirect comparisons (Section 3.5.1.6), the results are difficult to reconcile with the model predictions. At a minimum, the company base case position requires that OS results from the ITC are dismissed while simultaneously accepting the corresponding ITC results for relapse and assuming that relapse is an appropriate surrogate for OS. Consequently, while the EAG considers that the implied surrogate relationships are plausible, there are fundamental questions about the validity of model predictions.

Cure assumption

The concept of 'cure' and 'long-term' survivors and the associated assumptions are central to the cost-effectiveness estimates generated by the model and represent important structural assumptions. The cost-effectiveness of quizartinib is largely driven by the longer-term QALY benefits (and cost-offsets) attributed to the difference in the proportion of patients assumed to be functionally cured at 3 years (cycle 40). The company justifies the cure assumption applied in the model based on previous NICE TAs (TA523[21] and TA642[57]) which have allowed for functional cure in patients achieving long-term remission.

The EAG considers that the modelled cure assumption is clinically plausible. The concept of long-term survivors in *FLT3*+ AML is an accepted paradigm. Clinical advice received by the EAG suggests that relapses tend to occur early though also acknowledged that a residual risk remains long-term. As stated in the CS, cure assumptions have previously been accepted in several TAs including TA523, [21] and TA642.[57]

While the EAG accepts the concept of cure in principle, there are, significant uncertainties associated with this approach, specifically: (i) the time point at which it is considered appropriate to switch between the standard parametric models and SMR adjusted general population mortality (3 years in in the company base case) and (ii) the magnitude of the SMR which is subsequently applied (2 in the company base case). These issues are further discussed in later Section 4.2.6.5

Modelling of 2L

To incorporate the effectiveness of 2L AML treatments the base case model includes a series of health states that reflect the clinical pathway in this setting. Transition probabilities for these health states are primarily drawn from the ADMIRAL trial which evaluated the effectiveness of gilteritinib compared to salvage chemotherapy in patients with refractory or relapsed AML.[58] The EAG considers this approach broadly reasonable. However, the EAG considers how this has been implemented in the company's base case model as overly complicated and does not accurately reflect outcomes observed in the ADMIRAL trial.

The EAG considers there are three main issues with the company's approach. Firstly, the model retains the STM approach adopted in the modelling of 1L treatment. While not inherently incorrect, this approach is difficult to accurately populate without access to IPD. In the absence of IPD, the company makes the strong assumption that transition probabilities across 2L health states are time-invariant. This simplifies the structural relationships making the model tractable but also means that the model poorly reflects the treatment pathway. For example, relapsed and refractory patients in the company's model can continue to achieve (a 2L) remission throughout the entire time horizon. Secondly, and related to the use of time-invariant transition probabilities this approach fails to capture the possibility of patients achieving cure within the 2L setting. Evidence from the ADMIRAL trial suggests that patients can achieve sustained remission. Further, a cure assumption was accepted in TA642. Thirdly, the model structure does not allow patients to achieve remission following HSCT relapse and models outcomes differently to those who relapse without HSCT. The EAG is unclear why the company adopted a different approach to modelling outcomes in this group as they are modelled to receive 2L treatment in the same way as patients who relapse without HSCT. This approach also means that the PSM is not used to model outcomes in patients who relapse following HSCT. The EAG sees no reason why the PSM cannot be used to model outcomes in the post-HSCT relapse setting and notes that in the ADMIRAL trial, 48/247 (19.4%) in the gilterinib arm had previously received HSCT.

At the clarification stage, the EAG proposed an alternative approach to modelling 2L in which a nested PSM model is used to estimate outcomes for patients with relapsed and refractory disease (clarification question B1). Under this approach, patients transition to what is effectively a separate PSM that determines the QALY, and cost consequences associated with relapsed or refractory disease. This revised approach substantively simplifies the modelling of 2L treatment (requiring only two health states). It also enables evidence from the ADMIRAL trial to be more directly incorporated into the economic analysis overcoming the lack of access to IPD while simultaneously also allowing for a cure in the second-line setting.

The company's response to clarification question B1 included a revised model structure based on a nested PSM approach. Details of the company's preferred assumption are included in Appendix 8.5 along with a brief critique. Overall, the EAG considers the company's implementation of the PSM and its associated assumptions reasonable but notes issues regarding the modelling of treatment and disease management costs. Given the advantages of the PSM model structure, the nested PSM approach is the EAG's preferred model structure. In contrast to the scenarios presented by the company, the EAG prefers to also use the nested PSM to reflect outcomes in patients with relapsed disease following HSCT (Post-HSCT relapse).

4.2.3 Population

The modelled population is people with newly diagnosed *FLT3-ITD*+ AML who are eligible to be treated with intensive chemotherapy (i.e., standard cytarabine and anthracycline during induction and standard cytarabine consolidation chemotherapy). This population fully aligns with the marketing authorisation for quizartinib and the NICE scope.

The modelled baseline characteristics are based on adjusted the QuANTUM-First trial population effectively modelling the baseline characteristics of the RATIFY trial. A summary of the modelled baseline characteristics is reported in Table 16 and includes mean patient weight and body surface area (BSA) which were used to inform dosing associated with weight- and BSA-based therapies.

Table 16 Baseline patient characteristics of the modelled population (adapted from CS Table 45)

	Base case	Scenario analysis using direct trial estimates or ML-NMR
Female	54.4%	54.5%
Male	45.6%	45.5%
Age at start (years)	47.0	54.0
Mean bodyweight (kg)	[redacted]	[redacted]
Mean height (cm)	[redacted]	[redacted]
Mean BSA (m2)	[redacted]	[redacted]

Abbreviations: BSA: body surface area, ML-NMR: multilevel network meta-regression

In scenarios using either the trial data alone or where treatment effects are modelled using the ML-NMR, the modelled baseline population is informed by the unadjusted full QuANTUM-First population. This ensures that the modelled population characteristics align with the modelled treatment effects.

The NICE scope also listed people who are ineligible for HSCT as a subgroup of relevance, however no subgroups were considered in the CS. This subgroup was excluded based on the QuANTUM-First protocol in which people ineligible for HSCT were not a pre-specified subgroup and all patients

enrolled in the trial were eligible for intensive chemotherapy, aiming for HSCT as the primary therapeutic goal.

EAG comments

The EAG has substantive concerns about the population considered in the base case analysis. The RATIFY trial population, effectively modelled in the base case, is unlikely to reflect the population eligible for quizartinib in the NHS. Specifically, the inclusion criteria applied in the RATIFY trial imposed an age limit requiring patients to be ≤ 60 years old. Consequently, the RATIFY population is younger than the population eligible in practice. This was a major theme of TA523, where the EAG raised significant concerns about the generalisability of the RATIFY trial population. Moreover, starting age is an important driver of the model, and a low starting age will tend to favour more effective therapies. This is because life expectancy is longer in younger patients than older patients, and therefore, the benefits of cure are greater in a younger cohort.

The EAG considers the QuANTUM-First trial population more representative of the eligible NHS population. The QuANTUM-First eligibility criteria were less restrictive than those applied in RATIFY, requiring that patients only be under ≤ 75 years of age at the time of screening. This is likely to be broadly reflective of practice in the UK, with clinical advice suggesting that few patients over 75 would be eligible for intensive chemotherapy. The EAG also notes the company's own clinical advisors considered QuANTUM- First to be more representative.

The EAG acknowledges the company's motivation for modelling a RATIFY population to ensure consistency between modelled treatment effects (informed by the MAIC) and the modelled population but does not consider this an adequate justification for modelling the RATIFY population. The EAG's preference for QuANTUM-First also reflects their preferred approach to estimating the modelled treatment effects which is based on using the ML-NMR, see Section 3.5.1.6 for details.

4.2.4 Interventions and comparators

The modelling of all interventions and comparators aligns with established AML treatment phases. As outlined in Section 4.2.2, therapy administration is based on a 28-day treatment cycle and consists of three distinct phases: induction, consolidation and maintenance. Initial induction therapy aims to induce remission and consists of up to two cycles of treatment. Patients who achieve remission then move to the consolidation phase where they may receive further systemic therapy and/or HSCT. Consolidation therapy consists of up to four cycles of (systemic) treatment and may be further followed by maintenance treatment. The duration and eligibility criteria applied to maintenance treatment are dependent on the 1L treatment received.

4.2.4.1 Quizartinib

In line with the QuANTUM-First trial, and as per the marketing authorisation granted on 11th March 2024, the modelled intervention is quizartinib in combination with SC with or without HSCT, followed by quizartinib single-agent maintenance therapy.

The modelled dose of quizartinib in the induction and consolidation phases is 35.4 mg once daily, with each 35.4 mg dose administered as 2 x 17.7 mg capsules. Quizartinib is administered on days 8–21 of the induction and on days 6-19 of the consolidation phase. In the maintenance phase, the modelled dose of quizartinib is 26.5 mg once daily for 14 days and 53 mg once daily after that. Each 26.5 mg dose is administered as a single 26.5 mg capsule, while the 53 mg is administered as 2 x 26.5 mg capsules. The marketing authorisation of quizartinib permits up to 36 cycles of maintenance treatment, though the modelled duration is substantively shorter, see Section 4.4.2 for details. As per the marketing authorisation, quizartinib maintenance is modelled in both patients who do and do not receive HSCT.

4.2.4.2 Comparators

The NICE scope outlines several comparators according to the treatment phases (CS, Document B, Table 1):

- **Induction phase:** Established clinical management without quizartinib, including but not limited to midostaurin with daunorubicin and cytarabine.
- **Consolidation phase:** Established clinical management without quizartinib, including but not limited to midostaurin with cytarabine alone or in combination with other chemotherapy drugs, such as mitoxantrone, etoposide, or amsacrine.
- **Maintenance phase:** Established clinical management without quizartinib, including but not limited to midostaurin and azacytidine.

The model evaluates two comparator treatment regimens: i) midostaurin in combination with SC with or without HSCT and ii) SC (cytarabine and anthracycline induction, followed by standard cytarabine consolidation chemotherapy) with or without HSCT.

The modelled dosing regimen for midostaurin is 50 mg twice daily, with each 50 mg dose administered as 2 x 25 mg soft gel capsules. Midostaurin is administered on days 8–21 of induction and consolidation chemotherapy cycles and is then taken as a single-agent therapy for up to 12 cycles (CS, Document B, Table 65). Consistent with the marketing authorisation for midostaurin and in contrast with quizartinib, midostaurin maintenance therapy is only permitted in patients who have not received HSCT and is modelled as such. Patients who receive HSCT in the midostaurin arm of the model therefore receive no further systemic treatment.

The SC regimen is the same across all treatment arms and consists of induction and consolidation therapy only; SC does not include maintenance treatment. Patients who remain in remission following the consolidation phase therefore receive no further systemic treatment. Induction treatment comprises of cytarabine in combination with either daunorubicin or idarubicin followed by consolidation treatment with cytarabine. The dosing regimen modelled for SC in the induction phase is 200 mg/m^2 per day of cytarabine (days 1 until day 7) and either 60 mg/m^2 per day of daunorubicin or 12 mg/m^2 per day of idarubicin (days 1, 2 and 3). The dosing regime in the consolidation phase is 3.0 g/m^2 of cytarabine, every 12 hours on days 1, 3, and 5. All SC treatments are administered via intravenous infusion.

EAG comments

Deviations from the NICE scope

Several comparators explicitly listed in the NICE scope were not included in the company's economic model including mitoxantrone, etoposide, or amsacrine (see Section 2.3). The EAG considers these deviations from the NICE scope reasonable and that none of the excluded therapies represents routine practice in the NHS.

Relevance of SC

The company's model includes SC alone as a comparator in the economic analysis. Clinical advice to the EAG suggests that SC alone is rarely used in practice and that midostaurin plus SC is the first-line treatment for AML in the NHS. SC alone is used in only a minority of patients typically in patients who are contraindicated to midostaurin. For example, midostaurin would not be used in patients with significant gastrointestinal issues such as diarrhoea. This is consistent with current treatment guidelines which recommend the incorporation of midostaurin into first-line therapy for patients with *FLT3*-mutant AML. The EAG therefore considers the comparison to SC to be of limited relevance and that midostaurin-based regimens should be the main comparator for decision-making.

Omission of sorafenib

The company base case does not include sorafenib as a post-HSCT maintenance treatment. The CS justifies the exclusion of sorafenib stating that it is not licenced in this indication and has not been recommended by NICE. In recognition of the potential relevance of sorafenib, the company, however, does present a scenario analysis which includes sorafenib maintenance treatment (Section 5.3).

The EAG disagrees with the company and considers sorafenib a relevant comparator in the post-HSCT setting. Comparator treatments are not required to have a marketing authorisation, nor must they be recommended by NICE. Further, while the company is correct that sorafenib is not explicitly mentioned in the NICE scope it is also not explicitly excluded. The wording of the NICE scope is

inclusive and refers to established clinical management in the absence of quizartinib. The clinical case for sorafenib has been made in Section 2.2.3.2.

Post-HSCT treatment with quizartinib

As discussed in Section 2.1, it is unclear whether post-HSCT maintenance treatment with quizartinib is effective. In an exploratory subgroup analysis of 208 patients from the QuANTUM-First trial who received maintenance therapy following HSCT, quizartinib demonstrated no benefit, OS HR 1.62 (95% CI: 0.62 to 4.22).[59] This has led the FDA to restrict quizartinib approval and quizartinib is not indicated as maintenance monotherapy following HSCT within the USA. While the UK market authorisation does not place a similar restriction on using quizartinib following HSCT, the potential lack of effectiveness in this setting is an important consideration, particularly when evaluated in the context of the SORMAIN trial which demonstrated that sorafenib is an effective treatment in the post-HSCT setting.

As further discussed in Section 3.2.1.1, evaluating the effectiveness of quizartinib in the post-HSCT setting is complicated, as the QUANTUM-First trial was not designed to evaluate efficacy and safety outcomes in each treatment phase separately; comparisons of OS isolated to the post-HSCT setting break randomisation and are confounded by outcomes in prior treatment phases. Despite these complications, the EAG considers that further exploratory analysis could and should have been undertaken as requested in clarification question A9. Moreover, the EAG notes that the current company base-case model already makes strong assumptions about the effectiveness of treatment in the post-HSCT setting due to the implied surrogate relationships between CRc, HSCT and OS, see Section 4.2.2. The EAG therefore considers that the company should have also explored scenarios in which patients within the quizartinib model arm do not receive maintenance treatment (either proceeding to sorafenib or SC).

4.2.5 Perspective, time horizon and discounting

Consistent with the NICE methods guide,[60] the company's analysis adopted an NHS and Personal Social Services (NHS & PSS) perspective and discounted costs and benefits at a rate of 3.5%. The impact of alternative discount rates (0% and 6%) was assessed in scenario analysis.

A lifetime horizon of lifetime horizon of 53 years was chosen for the base-case analysis. Fewer than 0.1% of patients remain alive at this point in the model. The use of a lifetime horizon is therefore considered appropriate by the EAG and is sufficiently long to capture the health benefits and costs associated with quizartinib.

4.2.6 Treatment effectiveness and extrapolation

As discussed in Section 4.2.2, the company used a STM, where transitions between health states are explicitly modelled. Under this approach, state occupancy is determined by a set of transition probabilities which determine the likelihood of remaining in a health state or transitioning to one of the other health states.

Within the company's base case analysis, transition probabilities applied to model 1L treatment were informed by the QuANTUM-First trial and the MAIC analyses, while transition probabilities applied to model 2L treatment were primarily informed by the ADMIRAL trial supplemented by data from QuANTUM-First and other published values.

In scenario analysis where the QuANTUM-First trial population is modelled (rather than a RATIFY-like population), the ML-NMR is used instead of the MAIC analysis.

4.2.6.1 Transitions from Induction

The induction health state consists of two sub-tunnel health states induction 1 and induction 2. All patients begin in the induction 1 health state, with Cycle 1 marking the start of the induction phase.

Patients in the induction 1 substate can transition to the CR 1L, Induction 2, refractory or dead states. Patients in the induction 2 substate can transition to the CR 1L, refractory and dead states. Transition probabilities in this health state were time-invariant and were informed by data from QuANTUM-First (adjusted to a RATIFY-like population) and the MAIC analysis of CR. Table 17 summarises the transition probabilities applied to the induction 1 and induction 2 sub-states.

Table 17 Transition probabilities in the induction 1 and induction 2 health states (based on CS, Table 47 and company model)

Induction cycle	Transition to:	Transition probability, %					
		Quizartinib regimen		SC regimen		Midostaurin regimen	
		Inputs	Reference	Inputs	Reference	Inputs	Reference
First induction	Second round induction	Residual		Residual		Residual	
	First CR	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Based on the MAIC analysis (OR vs quizartinib=[redacted])
	Refractory	[redacted]	Weighted population ([redacted] of [redacted] patients had refractory disease within 28 days)	[redacted]	Weighted population ([redacted] of [redacted] patients had refractory disease within 28 days)	[redacted]	Assumed equal to quizartinib

Induction cycle	Transition to:	Transition probability, %					
		Quizartinib regimen		SC regimen		Midostaurin regimen	
		Inputs	Reference	Inputs	Reference	Inputs	Reference
	Dead	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Weighted population ([redacted] of [redacted] patients had CRc within 28 days)	[redacted]	Assumed equal to quizartinib
Second induction	First CR	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] achieved CRc)	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] achieved CRc)	[redacted]	Based on the MAIC analysis (OR vs quizartinib=[redacted])
	Refractory	Residual		Residual		Residual	
	Dead	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] died)	[redacted]	Weighted population (Of [redacted] patients remaining in cycle 2, [redacted] died)	[redacted]	Assumed equal to quizartinib

EAG comments

Timing of assessments in Induction 1 and Induction 2 states

Transitions from induction to CR 1L in both Induction 1 and Induction 2 states for quizartinib and SC were informed by the adjusted-QuANTUM-First data. To align with the model's 28-day cycle, is the company assume that Induction 1 in the model corresponds to the first 28 days of the trial. Patients who achieve CRc after this initial period are considered to have done so during the 2nd induction cycle (Induction 2). The EAG notes that this approach results in discrepancies between QuANTUM-First trial data and model predictions. Specifically, the modelled number of patients proceeding to Induction 2, differs significantly from that observed in the trial. The company's base case analysis predicts that [redacted] of patients will proceed to Induction 2 in the quizartinib arm and [redacted] in the SC arm which contrasts with the [redacted] and [redacted] observed in the unadjusted QuANTUM-First trial data. In response to clarification question B5, the company explained that although each induction cycle in the trial was 28 days long, this duration was allowed to vary by 3 days, meaning that the model and the trial are not perfectly synchronized.

The EAG is unconvinced by the company's explanation and considers it unlikely that a 3-day difference would so significantly impact the proportion of patients moving into 2nd induction. The EAG notes that the QuANTUM-First trial was designed such that additional time was allowed for recovery of blood counts or other reasons, both in the induction and consolidation phases. At the investigator's discretion, the 2nd induction cycle could start up to 60 days after Day 1 of the 1st

induction cycle to accommodate such needs. Consequently, patients could remain in the 1st induction cycle for up to 60 days. The EAG considers it more plausible that this discrepancy reflects the delayed assessment of CRc allowing for recovery of blood counts.

In response to clarification question B5, the company provided additional scenario analysis in which the model was calibrated to match the observed data from the QuANTUM-First trial. The EAG does not feel this scenario is helpful as it does not fully address the issue.

Assuming the same relative treatment effect for CR and CRc

In alignment with the QuANTUM-First trial and clinical practice, remission within the model is defined using the broader CRc definition (See Section 3.4.1.1). For the quizartinib and SC arms of the model, transitions from the induction health state were therefore informed by QuANTUM-First trial data on the proportion of patients achieving CRc. To model the relative effectiveness of midostaurin, an odds ratio for CR from the MAIC, as described in Section 3.5.1.3, was applied to the transition probabilities used for quizartinib regimen. This approach combines CRc data from QuANTUM-First with the relative treatment effect compared to midostaurin on CR. Consequently, the modelled outcome does not directly match the outcome evaluated in the MAIC, assuming instead that the treatment effect for CR can be transposed to CRc.

The EAG acknowledges that this assumption is due to the lack of CRc data for midostaurin and is not fully resolvable. However, it is unclear if it is appropriate to transpose relative treatment effects between these two definitions of remission. Considering the comparison between quizartinib and SC, evidence from the QuANTUM-First does not strongly support the equivalence of CRc and CR: the OR for CR is [redacted]) compared to OR [redacted]) for CRc.

Estimation of transitions for midostaurin

The EAG is concerned that the model does not appropriately integrate the evidence from the MAIC of CR. Within the economic analysis, the MAIC of CR acts upon the probability of transitioning to the CR 1L health state from the Induction 1 sub-state, Table 17. Applying the OR to the induction 1 sub-state does not align with the original purpose of the MAIC (or ML-NMR) analyses, which is to compare the overall rates of CR The probability of transitioning to the CR 1L health state from the Induction 1 sub-state only partially determines the overall remission rate applied in the model which is also determined by the transition probabilities applied in the induction 2 sub-state. Further because of how the Induction 1 and 2 states are structured, the primary effect of the applied OR is to drive the proportion of patients who receive a 2nd induction and not the overall rate of CRc.

The EAG considers this a structural issue relating to the design of the induction health state. The company base-case model does not directly incorporate evidence on the overall probability of CRc and chooses to explicitly model the 1st and 2nd induction periods. The EAG recognises this aligns with clinical practice but prevents the meaningful integration of evidence from the MAIC in the model. The EAG favours revising the induction health states to better accommodate the integration of the evidence on CR, see Section 6 for details.

4.2.6.2 Transitions from CR 1L

In the CR 1L health state, patients can transition to the Relapse 1L, HSCT 1L and death states (Figure 7, Section 4.2.2).

Transitions to HSCT

Transitions to the HSCT 1L health state reflect the proportion of patients that proceed to receive HSCT. The proportion of patients receiving HSCT was modelled as a function of CRc and was applied as a one-off transition in cycle 4. The modelled approach assumes that a fixed proportion of patients who achieve CRc will undergo protocol-specified HSCT, and that the transplantation rate remains unaffected by other factors, such as the treatment received.

The proportion of patients that proceed to receive HSCT was informed by data from QuANTUM-First and based on the pooled proportion of patients undergoing protocol-specified HSCT after achieving CRc, (presented in CS, Document B, Table 48). In response to clarification question B16, the company updated the proportion of patients undergoing HSCT from [redacted] to [redacted] This update corrected an error in the calculations presented in the CS.

Transitions from CR 1 to relapse1

Time-variant transition probabilities are applied to transitions from CR 1L to relapse 1L (summarised in CS, Document B, Table 49). Transition probabilities for the quizartinib model arm were derived using time-to-relapse from CRc using data from the QuANTUM-First trial adjusted to a RATIFY-like population. To account for the competing risks of HSCT and death events, the time-to-relapse curve was censored for both HSCT and death. Standard parametric models were fitted to the adjusted KM data. Model selection was based on the evaluation of hazard trends, visual fit, and fit statistics. Based on these criteria, the log-normal model was selected as the most appropriate and used in the base case analysis, see CS, Document B, Figure 25.

Transition probabilities for SC and midostaurin were derived using the quizartinib arm as a reference curve by applying HRs estimated from a MAIC analysis of CIR. Parameter values applied in the base case analysis are reported in Table 18. The MAIC analysis of CIR considers relapse events after CR (not CRc) and accounts for the competing risk of death as a competing event but does not censor for HSCT. The HRs applied are therefore based on analysis of a different outcome to that modelled in the

quizartinib arm and assumes that the HR generated from the MAIC of CIR can be transposed to the time to relapse from CRc outcome modelled. This approach also assumes PH which was tested using IPD from the QuANTUM-First trial. These tests suggested that the conditions for PH were not fully satisfied (see Figures 23 and 24 of CS).

Table 18 MAIC CIR HRs informing relapse from CRc (from CS, Table 55)

	HR	SE	95% lower CI	95% upper CI	Reference
Quizartinib vs midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	MAIC
Quizartinib vs SC	[redacted]	[redacted]	[redacted]	[redacted]	MAIC

Abbreviations: CI: confidence interval; CIR: cumulative incidence of relapse; CRc: composite complete remission: HR: hazard ratio: MAIC: matching adjusted indirect comparison; SC: standard chemotherapy; SE: standard error

Transitions from CR 1L to death

Death from CR 1L was modelled using a similar approach to relapse. Transition probabilities for the quizartinib model arm were derived using death from CRc using data from the QuANTUM-First trial adjusted to a RATIFY-like population. To account for the competing risk of HSCT, the death from CRc was censored for HSCT events. As with relapse from CRc, standard parametric models were fitted to the adjusted KM data with model selection based on the evaluation of hazard trends, visual fit, and fit statistics. Based on these criteria, the log-normal model was selected as the most appropriate and used in the base case analysis, see CS, Document B, Figure 31 of the CS.

Transition probabilities for SC and midostaurin were derived using the quizartinib arm as a reference curve by applying HRs estimated from a MAIC analysis of OS. Parameter values applied in the base case analysis are reported in Table 19. The MAIC analysis, from which HRs are derived, is based on OS from the time of randomisation and is not conditional on CRc. It also does not account for the competing risks associated with HSCT. The HRs applied are therefore based on analysis of a different outcome to that modelled in the quizartinib arm and assumes that the HR generated from the MAIC of OS can be transposed to OS from CRc. As for relapse from CR 1L, tests of PH conducted by the company and reported in Figures 29 and 30 of CS indicate that PH is violated.

Table 19. Comparative efficacy: MAIC OS HRs to inform death from CRc (from CS Table 57)

	HR	SE	95% lower CI	95% upper CI	Reference
Quizartinib vs midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	MAIC
Quizartinib vs SC	[redacted]	[redacted]	[redacted]	[redacted]	MAIC

Abbreviations: CI, confidence interval; CRc, composite complete remission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; SC, standard chemotherapy SE, standard error.

EAG comments

Overall survival as a surrogate for survival after CRc

The EAG considers the company's approach to modelling OS in the CR 1L health state fundamentally flawed. and completely inappropriate. The main assumption underpinning the company's approach is that relative treatment effects obtained from the MAIC of OS can be transposed to OS from CRc. This assumption is however clearly violated and demonstrably not supported by the observed data.

The drivers of relative OS in patients who achieve remission differ fundamentally from those of relative OS from the time of randomisation. Survival from the time of randomisation is a function of several potential mechanisms of benefit which principally include: the proportion achieving CR/CRc, the proportion receiving HSCT and post CR/CRc relapse rates. However, none of these mechanisms of benefit apply while a patient is within the CR 1L health state. Patients are already definitionally in remission, while OS events associated with relapse and HSCT are reflected elsewhere in the model. In so far as we observe differences in mortality this is likely driven by stochastic error (random chance) and the relative safety profile of the treatment regimens. Given the relative safety profiles of SC and quizartinib (see Section 3.2.4.4), the EAG would expect no meaningful differences in the OS rate. This aligns exactly with the observed trial data which shows that the KM curves for OS from CRc (censored for relapse and HSCT) almost overlap slightly favouring SC, see Figure CS, Figure 28.

Relative treatment effects obtained from the MAIC of OS are conceptually incompatible with what is being modelled. The EAG considers it impossible to approximate survival benefits in this context accurately. The EAG favours a simpler approach utilising the QuANTUM-First trial data and explores scenarios in Section 6.

Proportional hazards and application of hazard ratios

As outlined above, the company's approach to modelling relative treatment effects is to apply HRs either from the MAIC or ML-NMR (scenario analysis) to a reference survival curve. As detailed in Section 3.5.1.6, hazards are mathematically non-proportional at a marginal level in the presence of covariate effects (prognostic or effect-modifying). The company's approach to modelling relative treatment effects (using either a MAIC or ML-NMR) necessarily assumes the existence of covariate effects and therefore represents a fundamental inconsistency in the company's approach.

Using constant HRs and applying these constant HRs to baseline survival curves is inappropriate when hazards are non-proportional and are likely to result in significant bias. The magnitude of this bias can be illustrated by comparing the relapse from CRc survival curve for SC as generated using the company's approach (applying an HR) with an approach based directly on the QuANTUM-First trial data. Figure 8 illustrates this point. The pink curve represents the SC relapse from CRc survival curve generated using an HR, while the black curve fits a parametric model (lognormal curve) to the

KM survival data from the QuANTUM-First trial, adjusted to a RATIFY-like population. This demonstrates that the company's approach significantly underestimates survival outcomes for the SC arm.

Figure 8 Application of HRs on SC (placebo) arm

Abbreviations: CRc: composite complete remission; KM: Kaplan-Meier; HRs: hazard ratios

Moreover, it shows that outcomes for the midostaurin arm (generated using the MAIC HR and represented by the purple curve) are inferior to those based on the SC arm using the QuANTUM-First trial data. This is clinically implausible and demonstrates that the company's approach almost certainly overestimates the benefits of quizartinib relative to both SC and midostaurin.

The EAG considers the constant HRs generated by the MAIC and ML-NMR unsuitable for decision-making. The EAG favours integrating the results of the ML-NMR using the average survival curves for each treatment in the target population predicted within the ML-NMR (i.e. those presented in CS, Appendix M, Figure 1, and Figure 3) directly within the economic model. The EAG is unable to implement this analysis as it does not have access to the necessary IPD. The EAG therefore implements analysis using trial data from QuANTUM-First wherever able. This avoids this issue when considering the relative effectiveness of quizartinib and SC but does not address the problem of generating an appropriate survival curve for the midostaurin arm. As detailed in Section 3.5.1.6 and Section 4.2.3, the EAG does not consider the results of the MAIC relevant to the decision problem as the RATIFY population is not representative of NHS practice.

Extrapolation approach

The company's approach to extrapolation aligns with DSU TSD 14 and includes assessment of hazard trends, visual inspection of fit and evaluation of statistical fit.[61] However, the guidance provided in TSD 14 is not fully relevant to the current context. Within the vast majority of advanced cancer appraisals, fitting parametric models is done to extrapolate the observed survival data to make long-term predictions about survival beyond the observed data. This is not the case in the current appraisal. The structural cure assumption applied at 3 years means there is no requirement to extrapolate the observed data as follow-up is longer than 3 years. The sole purpose of the fitted parametric model in this context is to enable an HR to be applied to generate survival curves for midostaurin up to three

years when the cure assumption is applied. This purpose requires a different approach to the selection of the survival curves.

The EAG proposes two selection criteria relevant to this context. Firstly, the selected curve should accurately reflect the proportion of patients reaching the cure point in the observed data as this is a primary model driver of incremental benefits. Secondly, the selected curve should have a good visual fit to the observed KM data up to 3 years. This ensures that state occupancy before the cure point reflects the observed data. The EAG consider the evaluation of hazard trends or statistical fit less relevant to curve selection in this context. The EAG also considers it appropriate to evaluate fit to both arms. This is because the EAG considers it inappropriate to generate survival estimates for the SC arm using a HR given data is available separately from QuANTUM-First trial, see previous issue on proportional hazards. This implies that a common parametric model should be selected for the quizartinib and SC arms.

Evaluating the selected curves against the above criteria the EAG does not consider the preferred parametric fits appropriate. For the adjusted (RATIFY-like) population, the EAG prefers the generalised gamma to model relapse from CRc and the log-logistic for OS from CRc. For the unadjusted (QuANTUM-First) population, the EAG prefers the generalised gamma to model relapse from CRc and the Gompertz for OS from CRc. The EAG-preferred curves provide a better visual fit to the observed data and provide more accurate predictions of the proportion of patients reaching the cure point (see Table 20).

Table 20 Landmark analysis of company and EAG preferred parametric model

	Proportion of patients reaching cure point of 3 years					
	Relapse after CRc			**OS after CRc**		
	KM data	**Company preferred model**	**EAG preferred model**	**KM data**	**Company preferred model**	**EAG preferred model**
Adjusted (RATIFY-like) population						
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted (QuANTUM-First) population						
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Assumes company's preferred curve for quizartinib is applied to both arms

4.2.6.3 Transitions from HSCT 1L

In the HSCT 1L health state patients can transition to the post-HSCT 1L relapse and death states

Transitions to post-HSCT 1L

Transition from the HSCT 1L to post-HSCT 1L relapse were informed by data from the QuANTUM-First population using time invariant transition probabilities (see CS, Document B, Table 51). Separate transition probabilities were modelled for SC and quizartinib to reflect the effectiveness of post-HSCT maintenance therapy. For the midostaurin model arm, transition probabilities were assumed equivalent to SC reflecting the base case assumption of no post-HSCT maintenance therapy following either SC or midostaurin.

Transitions to death

Transition from HSCT 1L to death were similarly informed by data from the QuANTUM-First trial but in contrast to transitions to the post-HSCT 1L state used a time-variant approach. These were derived from post-protocol-specified HSCT survival data from QuANTUM-First trial adjusted to a RATIFY-like population, censored for relapse (CS, Section B.3.3.3.3). Independent parametric survival curves were fitted to the quizartinib and SC KM data. The generalised gamma model was selected based on visual fit for the SC arm and the Gompertz distribution for the quizartinib arm. For comparative efficacy, post-HSCT survival for midostaurin was assumed to be equivalent to the SC arm. The company however conducted a scenario analysis considering sorafenib as the post-HSCT maintenance treatment in the midostaurin arm, with the post-HSCT survival for sorafenib set equal to the quizartinib arm.

EAG Comment

Inconsistent approach to modelling transition probabilities

The EAG does not understand the inconsistent approach to modelling transitions in the HSCT 1L health state. Specifically, why the company has used to time invariant transition probabilities to model relapse events when a time-varying approach was used to model OS events. In response to clarification question B8, the company stated that this was due to the small number of relapse events. The EAG, however, does not understand this justification and there similarly few OS events. The EAG therefore prefers a consistent approach using time-varying transition probabilities for both relapse and OS transitions.

Approach to extrapolation

The company fits different parametric survival models to the quizartinib and SC arms. This approach is inconsistent with the recommendations in NICE DSU TSD 14 and it is unclear why this unusual approach has been adopted. In response to clarification question B6, the company states that:

"Although the PH assumption (PHA) holds for the post-HSCT survival curves based on the PHA statistical test, independent models were chosen to use to better fit each dataset"

This response, however, appears to misunderstand the DSU guidance. Using the same type of parametric survival function does not impose the PH hazards assumption except when using an exponential model. The DSU guidance advises that the same type of parametric model should be used in both model arms and that exceptions to this should be clearly justified. This ensures that modelled survival follows similar trajectories and does not assume fundamental differences in hazard trends. The EAG considers the company's approach unjustified and prefers to use the generalised gamma function to model both treatment arms when modelling the adjusted population.

4.2.6.4 2L transitions

In the company's base case analysis, 2L treatment is modelled using an STM approach comprising of the following health states.: Relapse 1L, Refractory, Complete remission in 2L (CR2), Relapse 2L, HSCT 2L, and Post-HSCT maintenance 2L. As described in Section 4.2.4, the EAG considers this approach overly complicated and prefers a simpler approach based on using a nested PSM to model 2L treatment. The EAG therefore only provides a high-level summary and brief critique of the company's base case approach. Table 21 summarises the possible 2L transitions and the data used to inform the transition probabilities. Transition probabilities in the 2L health states are primarily informed by data from the ADMIRAL trial which evaluated the efficacy of gilteritinib compared to salvage chemotherapy in patients with relapsed or refractory *FLT3*+ AML.[58] Where data was used from ADMIRAL transition probabilities were based on pooled data from the gilteritinib and salvage chemotherapy arms. Data from ADMIRAL was also supplemented by data from QuANTUM-First and Styczynski et al.,[62] see Table 21. The latter investigated mortality following HSCT in a large cohort of leukaemia patients. Transitions within the second line setting were all modelled as time-invariant with the partial exception of HSCT 2L and HSCT 2l Recovery states which were modelled as a series of tunnel states.

Table 21 Summary of 2L transitions

Transition from:	Transition to:	Source	Assumptions
Refractory	Refractory	Residual	The same TPs applied to all regimens.
	CR 2L	ADMIRAL	
	Death	ADMIRAL	
Relapse 1L	Relapse 1L	Residual	i) The same TPs applied to all regimens for transition from Relapse 1L to CR 2L ii) The same TP applied to midostaurin and quizartinib
	CR 2L	ADMIRAL	
	Death	QuANTUM-First	
Post HSCT relapse 1L	Post HSCT relapse 1L	Residual	TPs are treatment specific.

	Death	QuANTUM-First	
	Death	QuANTUM-First	
CR 2L	CR 2L	Residual	The same TPs applied to all regimens
	Relapse 2L	ADMIRAL	
	HSCT 2L	ADMIRAL	
	Death	ADMIRAL	
Relapse 2L	Relapse 2L	Residual	Assumed the same as the transition probability from Relapse 1L to Death.
	Death	QuANTUM-First	
HSCT 2L/HSCT 2l Recovery	Subsequent tunnel state	Residual	Tunnel states
	Death	Styczynski et al	
Post-HSCT 2L recovery	Post-HSCT 2L recovery	Residual	None
	Death	Styczynski et al	

Abbreviations: CR: complete remission; CR2: complete remission on second line therapy; 2L: second line, HSCT: allogeneic haematopoietic stem cell transplantation; TP: transition probability

EAG comments

The EAG finds the company's approach to modelling 2L transitions confusing and overly complicated. As noted in Section 4.2.2, the use of time-invariant transition probabilities inadequately reflects clinical reality and ignores the possibility of cure in a 2L setting. Additionally, the EAG identifies multiple inconsistencies in the company's methodology.

It is unclear why different transition probabilities are applied to the Refractory, Relapse 1L, and Post-HSCT relapse 1L health states, and why treatment-specific transition probabilities are used for the Post-HSCT relapse 1L state but not for the Relapse 1L state. The EAG also questions the data sources selected for these probabilities. For example, it is unclear why transitions from the Relapse 1L health state to death are informed by QuANTUM-First, while transitions from Relapse 1L to CR 2L are informed by ADMIRAL. The EAG questions the appropriateness of mixing data sources in this way.

The EAG believes the company's approach should have been thoroughly justified, especially where different transition probabilities are assumed for each treatment regimen. If the STM approach is retained, the EAG recommends simplifying the model by combining the Refractory, Relapse 1L, and Post-HSCT relapse 1L health states. This simplification would significantly reduce complexity and increase the data available for populating the model.

4.2.6.5 Modelling cure

As described in Section 4.2.2, the model allows 'functional' cure in patients experiencing long-term remission (i.e., patients remaining in the CR 1L and HSCT 1L health states) beyond 3 years. Functionally cured patients were assumed no longer at risk of relapse but were assumed to experience

excess mortality (relative to the general population). Aligning with previous appraisals TA523 and TA642, excess mortality was captured by applying an SMR of 2 to general population mortality rates following the cure point. The excess mortality HR was applied after the cure point (at three years) and was only applied to patients in the CR 1L and HSCT 1L health states. Patients in the Refractory, Relapse (1L and 2L) and Post-HSCT relapse (1L) health states were not considered to be curable.

EAG comments

As discussed in Section 4.2, the EAG is generally satisfied with the company's approach to modelling cure but considers there to be uncertainties regarding both the timing of the cure point and the adjustment factor (SMR) applied.

Uncertainty in the timing of cure

The structural assumption of cure at 3 years is not supported by evidence from QuANTUM-First and relies on precedent from previous appraisals (TA523 and TA642). The company have not statically modelled cure (e.g. using a mixture-cure model) using data from QuANTUM-First or provided any other evidence to support the selected cure point. Evaluation of the KM survivor functions for both quizartinib, and SC demonstrates ongoing evidence of both deaths and relapses beyond the 3-year cure point. This suggests that surviving patients remain at risk of AML-related relapse and associated mortality, indicating that 3 years may be too early to establish that patients are functionally cured. In TA523, a cure point of 6.2 years was accepted based on the maximum follow-up of the RATIFY trial, and committee discussions noted that clinicians typically consider patients cured after 5 years. This is substantially longer than the 3 years assumed in the base case analysis. However, committee deliberations and clinical expert advice received in TA642 support the adoption of a 3-year cure point. Clinical advice suggested that most relapses occur within 12 months and that it is clinically plausible to assume that patients alive after 3 years are cured. The EAG considers there to be substantive uncertainty associated with the adopted cure point, this issue is, however, not explored further given the other substantive issues with the company's economic analysis.

Uncertainty in SMR

The decision to adjust general population mortality rates in AML survivors appears supported by clinical evidence which suggests that patients remain at higher risk of other health conditions which may increase mortality rates above that of the general population, including secondary or relapsed cancer, late complications following an HSCT, or cardiovascular disease following an anthracycline (such as daunorubicin and idarubicin). The SMR of 2 applied the base case analysis was informed by committee-preferred assumptions in TA523. However, this value was not informed by data (from RATIFY or other sources) but was instead elicited from seven clinical experts. Reflecting on this assumption, the committee discussions noted the high uncertainty associated with this parameter. It is also important to highlight that the committee's consideration of the SMR reflected the cure point of

6.2 years as discussed in TA523. It is unclear whether it is appropriate to apply the same SMR when a different cure point of 3 years is being used.

4.2.6.6 Adverse events

The analysis included AEs of grade ≥3 with an incidence of ≥5%. These were unadjusted for difference in age distribution between trials for quizartinib and SC. All AEs were assumed to occur within the first model cycle. Incidence rates were sourced from the QuANTUM-First trial for quizartinib and SC, and the RATIFY trial for midostaurin. These rates are presented in CS, Document B, Table 60.

Graft-versus-host disease (GVHD), the most severe complication linked to HSCT, was also modelled, and applied in the first cycle of HSCT (1L and 2L). GVHD rates were sourced from the QuANTUM-First trial for quizartinib and SC. The incidence of GVHD for midostaurin was assumed to be 39%, based on Wingard *et al.*[63] as per TA523.

EAG comment

The EAG considers the company's approach to modelling AEs to be broadly appropriate and to accurately reflect the burden of AEs associated with each treatment regimen.

4.3 Summary and EAG critique of health-related quality of life evidence within the company's submitted economic evaluation

4.3.1 Searches

The CS, Appendix H contained a description of the search methods and search strategies to identify studies reporting utility data in adults with *FLT3*+ AML.

In general, the EAG was satisfied that a comprehensive search was performed to identify studies reporting on health state utility values for this population. However, the original searches in the November 2023 company submission were not updated for the March 2024 or the April 2024 company submissions. Therefore, more recent studies would not have been identified by the searches presented. The EAG appraisal of the searches can be found in Appendix Table 41.

The company approach to study selection for all reviews which inform the economic evaluation is described in Section 4.1.2. The SLR of HRQoL identified 10 relevant studies for inclusion (CS, Appendix H, Table 5). Three of these studies related to data specifically collected in the UK (CS, Appendix H, Table 6).

4.3.2 Collection of HRQoL /utility data from clinical trials (i.e. QuANTUM-First)

Patient Reported Outcomes (PRO) data were collected from participants in the QuANTUM-First trial using EORTC-QLQ-C30 and EQ-5D-5L questionnaires at each trial visit for both treatment arms. The schedule of PRO assessments taken in QuANTUM-First was as follows:

[redacted]Details of the statistical analysis of PRO data collected in QuANTUM-First were not reported in the CS but were provided in the PRO report included in the reference pack.[64] PRO data was analysed using a mixed model for repeated measures (MMRM) analysis. The main model included baseline score, treatment, time and an interaction term of treatment and time.

The overall compliance rate for EQ-5D-5L assessments by visit ranged from [redacted] to [redacted] and was markedly lower in the consolidation phase compared to the induction and maintenance phase. No imputation of missing values was undertaken in the analysis of EQ-5D-5L, data were therefore analysed assuming missing values were missing-at-random (MAR).

PRO collected in QuANTUM-First were not used in the economic model. The company argues that the exploratory nature of the PRO analyses necessitates that utility values from the literature be applied in the model (CS, Section B.3.4.1). At the clarification stage (Question B11), the EAG requested that the company provide further rationale for excluding HRQoL values from the trial and to conduct a scenario analysis using the PRO data collected in the QuANTUM-First trial. The company's response to clarification question B11 reiterated arguments that HRQoL data was collected as an exploratory endpoint and is therefore unsuitable for use in the economic model. The company also outlined that due to the design of data collection in the QuANTUM-First trial, which did not include data collection after discontinuation, collected PRO data cannot reflect the impact of relapsed and refractory disease on HRQoL.

Scenario analysis provided by the company updates the economic model to utilise trial-derived utility values in the induction, consolidation, maintenance, HSCT 1L and HSCT 2L health states. Utility values applied in other health states continued to be informed by published values in line with the company base case, see Section 4.3.3 for details.

EAG comments

The EAG has concerns regarding using the utility values reported in the literature given the availability of EQ-5D data collected in QuANTUM-First. The NICE reference case guidance recommends using EQ-5D reported by patients, from relevant clinical trials, and that only where they

are unavailable should literature-based values be used.[60] The value set used in the company's base case analysis is consequently inconsistent with the NICE reference case.

The company notes in its submission that the value set adopted in the base case analysis aligned with TA523 and is therefore consistent with previous appraisals in AML (CS, Section B.3.4.1. p.192). While it is correct that published utility values were used in TA523, this was justified as trial-based values were unavailable. Further, trial-based values were used (where available) in TA642.

Limited details on the methods used to generate the value set were provided in the company's response to clarification question B11. The EAG therefore cannot validate the methods used and it is unclear whether or how the EQ-5D-5L values collected in QuANTUM-First have been mapped to EQ-5D-3L, as required by the NICE reference case. The reference to UK index score (Hernández Alava Table 39; page 86 in clarification response) is ambiguous. The EAG observes that the provided trial-based values are substantially higher than those obtained from published sources. These discrepancies could be due to various factors, including the possibility that the values were not mapped to the EQ-5D-3L, as utility values based on the EQ-5D-5L are generally higher. Clarification on how the trial-based value set was generated, specifically including the methodology used for mapping values to the EQ-5D-3L, may help to explain the discrepancies.

4.3.3 Health state utilities

Health state-specific utility values incorporated in the base case analysis were derived from several sources. Table 22 provides a summary of the utility values used within the model for the base-case analysis.

The utility values assigned to several states were based on utility values used in TA523 and clinical expert opinion was used to map these values to health states in the model where health state descriptions were not aligned.

The company made several assumptions to map utility values from TA523 to the health states used in their analysis. As was the case in TA523, the utility value for the HSCT 1L state was derived from the average of three relevant health states: HSCT treatment, HSCT recovery, and post-HSCT recovery. Similarly, the utility values for the 2L health states did not have direct counterparts in the TA523 model. Consequently, the company assumed that the utility values for the 2L health states were 90% of the respective 1L health states from TA523. This assumption was validated by the company's clinical expert.[65]

Patients who were functionally cured (CR 1L and HSCT 1L health states after cycle 40) were assumed to have HRQoL consistent with patients of the same age in the general population. Age- and gender-matched utilities were estimated from the Health Survey for England 2014 dataset. These

values were estimated on a per-cycle basis to allow the model to capture the gradual decline in HRQoL associated with ageing.

Table 22 Summary of utility values used in the model (Source: Table 62, CS)

Utility state	Utility values	Reference
Induction	0.648	Uyl-de Groot et al. 1998[66] in Tremblay et al. 2018 [67] and TA523[68]
Refractory	0.530	Pan et al. 2010[69] in Tremblay et al. 2018 [68]
Consolidation	0.710	Batty et al. 2014[70] in Tremblay et al. 2018 [68] and TA523[68]
Maintenance	0.810	Batty et al. 2014[70] in Tremblay et al. (2018) [67] and TA523[68]
First CR	0.830	Leunis et al. 2014[71] in Tremblay et al. (2018)[67] and TA523[68]
Relapse1	0.530	Pan et al. 2010[69] in Tremblay et al. (2018)[67] and TA523[68]
Second CR	0.747	Assumption: 90% of the utility for the 'First CR'
Relapse2	0.477	Assumption: 90% of the utility for the 'Relapse1'
HSCT 1L	0.750	Source for Algorithm—Crott et al. (2010)[72] Source of QLQC30 data—Grulke et al. (2012)[73] Calculation in Midostaurin STA[21] Average of following utility values from TA523: SCT treatment (0.613), SCT recovery (0.810), and Post-SCT recovery (0.826)
HSCT 2L	0.552	Source for Algorithm—Crott et al. (2010)[72] Source of QLQC30 data—Grulke et al. (2012)[73] Calculation in Midostaurin STA[21] Assumption: 90% of the utility value from SCT treatment health state (0.613) in TA523[68]
HSCT recovery 2L	0.729	Source for Algorithm—Crott et al. (2010)[72] Source of QLQC30 data—Grulke et al. (2012)[73] Calculation in Midostaurin STA[21] Assumption: 90% of the utility value from SCT recovery health state (0.810) in TA523[68]
Post-HSCT 2L maintenance	0.743	Source for Algorithm—Crott et al. (2010)[72] Source of QLQC30 data—Grulke et al. (2012)[73] Calculation in Midostaurin STA[21] Assumption: 90% of the utility value from Post-SCT recovery health state (0.826) in TA523[68]

4.3.3.1 EAG comments

Appropriateness of selected utility values

For TA523, using utility values from the literature was necessitated as the RATIFY trial of midostaurin compared to SC did not collect PROs. More recently in TA642, health state utilities were based on the relevant trial (ADMIRAL).

In response to clarification question B11, the company provided some trial-based health state utility values. Table 23 highlights differences between these values and those from TA523.

Table 23 Summary of utility values for cost-effectiveness analysis used in the CS base case and scenario analysis using QuANTUM-First trial data (adapted from response to clarification question B11, Table 39)

	Utility values	
Health state/treatment phase	**CS base case**	**QuANTUM First**
Induction	0.648	[redacted]
Consolidation	0.710	[redacted]
Maintenance	0.810	[redacted]
HSCT 1L	0.750	[redacted]
HSCT 2L	0.552	[redacted]

As per the previous EAG critique in TA523, the utility values for induction treatment and HSCT are comparatively low and possibly unrealistic. None of these values from the literature specifically refer to untreated *FLT3 ITD+* AML patients, and several were informed by TTO exercises conducted with the general public. For example, the utility values applied during the consolidation and maintenance phase are from Pan *et al*.[69] and were based on TTO values elicited from the general public. However, the health states described in the TTO exercises pertained to myelodysplastic syndrome, not AML. The AML literature offers numerous alternative utility values that could have been considered, and the use of these values should have been explored through sensitivity or scenario analyses. The company rational for selecting these values, other than noting that they were previously accepted as appropriate in TA523, remains unclear.

HRQoL in functionally cured patients

The EAG is concerned the utility values applied to cured patients may overestimate HRQoL in these patients. The assumption that functionally cured patients experiences the same HRQoL as the general population results in a marked jump in the HRQoL estimates at 3-years in patients who have received HSCT. The use of general population HRQoL estimates is not internally consistent with the excess mortality applied for functionally cured patients to OS. Given that functionally cured patients are assumed to be at higher mortality risk than the general population, the EAG concluded that it would appear reasonable to assume that functionally cured patients would also have a lower HRQoL than the general population. Alternative assumptions have been explored by the EAG in Section 6.1.

Effect of adverse events on HRQoL

The company did not explicitly apply disutilities relating to AEs in the original base-case model, assuming instead that the health state utility values used in the model incorporate the impact of AEs experienced during treatment. The only disutility incorporated in the model was for GVHD, as per the EAG recommendations from NICE TA523. The disutility for GVHD (-0.173) was applied to the proportion of patients experiencing GVHD (assuming a duration of 57 days) and was applied on entry to the HSCT 1L and HSCT 2L health states.

The adverse events of special interest, specifically QT prolongation (as mentioned in CS, Section B.2.10.7), are more frequently observed with quizartinib than with standard care (CS, Table 41). Any disutility associated with QT prolongation, which requires monitoring costs and potentially results in dose modification and correction of electrolyte abnormalities, is likely to have only a minor impact on cost-effectiveness estimates.

Finally, the EAG notes that the company's approach will not capture any disutility associated with subsequent treatments (e.g., sorafenib and gilteritinib). In TA642, the calculated AE disutilities for gilteritinib was -0.211 and for salvage chemotherapies was -0.143. The impact of this on cost-effectiveness estimates is not likely to be important.

4.4 Resources and costs

The CS (Section B.3.5) provided a description of resource use and costs applied in the model. This comprised of drug acquisition and administration costs, treatment-specific monitoring costs, HSCT procedure costs, disease management costs, AE costs and terminal care costs. The company predominately informed healthcare resource use from the (QuANTUM-First and ADMIRAL trials as well as the previous appraisal of midostaurin (TA523; with many inputs originally from TA399 azacitidine.[74] Unit costs were informed by NHS Reference Costs 2021-2022[75], NIHR interactive costing tool (iCT),[76] eMIT[77] and the British National Formulary (BNF).[78]

4.4.1 Searches

An SLR was conducted to identify healthcare cost and resource use data associated with patients with newly diagnosed *FLT3-ITD*+ AML from the published literature. This is described in CS, Appendix I.

Appropriate and comprehensive searches were undertaken to identify studies of costs and resource use for this population. However, as the searches had not been updated since May 2023, more recent studies would not have been identified. The EAG appraisal of the searches can be found in Appendix Table 42.

Study eligibility criteria are described in CS, Appendix I. The company approach to study selection for all reviews which inform the economic evaluation is described in Section 4.1.2.

The SLR identified 14 unique studies of which nine publications had data relevant to the UK (four were UK-based and five were international studies that included patients in the UK). All the studies reported outcomes in patients with *FLT3*+ AML, however, none reported outcomes specific to the *FLT3 ITD*+ AML population. Four of the identified studies were cost and resource use studies, three were cost-effectiveness analyses, and two were clinical trial studies reporting healthcare resource utilisation.

4.4.2 Drug acquisition, administration, and procedure costs.

The drug acquisition costs were split into two sections: First-line treatment and subsequent treatment. Costs were calculated based on the drug costs per treatment regimen using the eMIT database[77] and the BNF.[78]

4.4.2.1 First-line treatment

The quizartinib regimen, the midostaurin regimen and the SC regimen are administered 1L. These regimens are applied in the induction, CR 1L, HSCT 1L health states. Only quizartinib acquisition costs (as monotherapy) are applied in the HSCT 1L state as midostaurin is not licensed or recommended in post-HSCT population and the SC regimen does not include maintenance treatment. Based on data from QuANTUM-First only [redacted] (CS, p.198) of patients were assumed to initiate post-maintenance treatment with quizartinib. The remainder receive no further pharmacological treatment.

Table 24 describes the pack size and pack costs for each intervention in 1L in the model. A patient access scheme (PAS) is available for quizartinib consisting of a simple discount of [redacted], reducing associated acquisition costs to [redacted] per 28-pack of 17.7mg tablets and [redacted] per 56-pack of 26.5mg tablets. Midostaurin and sorafenib are also subject to confidential commercial arrangements not included in the company's analysis. Analyses inclusive of all confidential pricing arrangements are included in a confidential appendix to the EAG Report.

Table 24 Summary of pack size and cost for each intervention in 1L

Treatment	Pack size	Pack cost	Cost per mg	Reference
Quizartinib	17.7 mg x 28	[redacted]	[redacted]	Daiichi Sankyo 2023
	26.5 mg x 56	[redacted]	[redacted]	Daiichi Sankyo 2023
Midostaurin	25 mg x 56	£5,609.94	£4.01	BNF 2023
Cytarabine	500 mg/vial x 5	£16.44	£0.01	eMIT 2023
Daunorubicin	20 mg/vial x 10	£715.00	£3.58	BNF 2023
Idarubicin	10 mg/vial x 1	£138.00	£13.8	eMIT 2023
Sorafenib	200mg x 112	£822.10	£0.11	eMIT 2023

Abbreviations: Admin: administration route; BNF: British National Formulary; eMIT: electronic market information tool; IV: intravenous; 1L: first-line treatment.
References: BNF, 2023,[78] eMIT, 2023,[77] Daiichi Sankyo, 2023[79]
Notes: the quizartinib price provided is the PAS price

Patients receive treatment per the assigned treatment regimen for induction, consolidation, and maintenance phases (CS, Document B, Table 65). In the context of anthracycline selection, the

percentages were derived from the QuANTUM-First trial. Midostaurin is solely associated with daunorubicin, as per the RATIFY trial. Relative dose intensity (RDI) refers to the proportion of the intended dose which was administered in practice. For quizartinib and SC, RDI was extracted from QuANTUM-First while RDI for midostaurin was taken from the NICE TA523. The company model incorporates the cost of drug wastage by rounding the quantity of drug required for each administration to the nearest whole pill or vial and using this quantity to calculate the corresponding drug cost.

Quizartinib and midostaurin are oral treatments and were assumed to be associated with no additional administration. The unit administration costs for SC and intravenous (IV) therapy were sourced from the National schedule of NHS costs 2021/22.[75] SC treatment and IV therapy administration costs were applied for each administration of the treatment per cycle (e.g. cytarabine is administered intravenously seven times during cycle 1).

Drug acquisition costs applied in the company model were based on RDI, state occupancy and time on treatment. Time on treatment was calculated using observed data from QuANTUM-FIRST by summing time on treatment across the induction, consolidation, and maintenance phases see Table 25 In line with this approach, treatment costs were only applied for [redacted] cycles in patients who did not proceed to HSCT and [redacted] cycles in patients who received HSCT.

Table 25 Mean treatment duration for the 1L treatment (CS Table 66, page 201)

	Mean treatment duration (cycles)					
	Quizartinib		SC		Midostaurin	
	Inputs	Reference	Inputs	Reference	Inputs	Reference
Induction	[redacted]	QuANTUM-First unadjusted	[redacted]	QuANTUM-First unadjusted	[redacted]	Assumed same as quizartinib
Consolidation	[redacted]		[redacted]		[redacted]	
Maintenance, patients without HSCT	[redacted]	Daiichi internal analysis T.5.1.3_EXPO_SAS	0.00	SC is not administered post-HSCT	[redacted]	Midostaurin SmPC
Maintenance, patients with HSCT	[redacted]		0.00		0.00	Midostaurin is not licensed after HSCT

Abbreviations: HSCT: allogeneic haematopoietic stem cell transplantation; CSR: clinical study report; SC: standard chemotherapy; SmPC: summary of product characteristics; 1L: first-line treatment.
References: Daiichi Sankyo, 2022 [27]; Novartis Pharmaceuticals UK Limited, 2023 [80]; NICE, 2018 [20]; NHS England, 2023 [81]; Daichi Sankyo, 2024 [82]

In a scenario analysis exploring the use of sorafenib in a post-HSCT setting the duration for sorafenib was informed by data from the Phase II trial (SORMAIN) which investigated the efficacy of sorafenib as maintenance therapy after HSCT for *FLT3*+ AML patients was used (CS, p.201).[43] The mean duration of treatment was not reported for the SORMAIN trial, the company therefore used the median treatment duration of 34.6 weeks (equivalent to 8.65 28-day cycles) in the scenario analysis.

EAG comment

The EAG considers the company's approach to estimating drug acquisition costs and time on treatment flawed. There are three issues with their approach.

Firstly, the company's approach does not consider that RDI differs substantively across treatment phases. As reported in the CSR, RDI is [redacted] and [redacted] in the induction, consolidation and maintenance phases respectively for quizartinib (CS, Table 34, p. 112-3). Therefore, application of a single mean RDI across all treatment phases does not accurately reflect the variation in RDI.

Secondly, the modelled meantime on treatment is based on the restricted mean as follow-up in the maintenance phase is incomplete, see response question B12. Restricted means reflect the average (mean) survival time within the observed period and account for censoring due to incomplete follow-up. Where follow-up is incomplete (i.e., all events have not occurred), the restricted mean underestimates the unrestricted mean, representing the mean survival time if all events had occurred. The unrestricted mean should be used to estimate time on treatment and while not directly observable where follow is incomplete can be estimated by appropriate extrapolation of the observed data. The company's approach will underestimate the total time on treatment and consequently underestimate drug acquisition, administration and monitoring costs, particularly those associated with quizartinib maintenance treatment.

Thirdly, treatment costs in the economic model are applied in the induction, CR 1L and HSCT 1L health states and therefore occupancy of these states is the proportion of the modelled cohort who are on treatment. The model however also cross references with the time on treatment data depicted in Table 25 and only applies costs in model cycles before the mean time on treatment is reached. This approach is fundamentally incorrect and double counts the impact of relapse, HSCT and OS events when estimating time on treatment. Time on treatment as observed in the trial reflects discontinuation for a variety of reasons which include medical events such as relapse, HSCT and OS, which prevent patients from receiving treatment, and other types of events such as patient choice, adverse events, and loss to follow-up. The treatment costs estimated in the economic model account for relapse, HSCT and OS events via state occupancy but also do so again when referencing time on treatment. This approach will again significantly underestimate drug acquisition, administration and monitoring costs, particularly those associated with quizartinib maintenance treatment.

The EAG's preferred approach to modelling time on treatment is summarised in Table 26. The EAG is unable to implement this within the economic model as it does not have access to all the necessary. The EAG emphasises the implementation of the approach should account for the population being modelled i.e. data should be adjusted to the population being modelled.

Table 26 Summary of EAG's preferred approach to modelling time on treatment

	Quizartinib	SC	Midostaurin	Justification for approach
Induction	Use state occupancy to determine the proportion of patients receiving treatment.			The proportion receiving treatment reflects the proportion modelled to have 2nd induction.
Consolidation	Apply lump sum cost on entry to CR 1L and HSCT 1L health states using mean time on treatment in the consolidation phase observed in QuANTUM-First.		Assume mean time on treatment is the same for quizartinib and midostaurin	State occupancy cannot accurately reflect time on treatment because the model cannot fully capture the time of HSCT. No need to use full time on treatment curve as acquisition, administration and monitoring costs are unaffected by discounting. Ensures the model fully reflects trial data. The assumption of equal time on treatment for quizartinib and midostaurin implies the risk of relapse, HSCT and death are the same across quizartinib and midostaurin for the first four weeks following CRc.
Maintenance without HSCT	Use the relevant time on treatment curve from QuANTUM-First censored for relapse, HSCT and death.	NA	Assumed the same as quizartinib but truncated survival curve at 12 months to reflect SmPC	Avoid double counting of Relapse, HSCT and death events. Ensure the model fully reflects trial data and captures discontinuations for reasons other than relapse, HSCT and death. The assumption of equal time on treatment for quizartinib and midostaurin (up to 12 months) implies that both treatments are equally tolerated.
Maintenance with HSCT	Use relevant time on treatment curve from QuANTUM-First censored for relapse, HSCT and Death.	NA	NA	Avoid double counting of relapse, HSCT and death events. Ensure the model fully reflects trial data and captures discontinuations for reasons other than Relapse, HSCT and death.

Abbreviations: CR: complete remission; CRc: composite complete remission; HSCT: allogeneic haematopoietic stem cell transplantation; NA: not applicable; SmPC: summary of product characteristics; 1l: first-line treatment

4.4.2.2 Subsequent treatment

All patients with relapsed or refractory disease were assumed to receive subsequent treatment consisting of either FLAG-Ida or gilteritinib. Subsequent treatment costs were applied to entry to the refractory, relapse 1L and post-HSCT relapse 1L health states. Costs and dosing schedules modelled for subsequent treatments are summarised in CS, Document B, Table 67 and Table 68. The dosing schedule was assumed to be the same for the refractory, relapse1, and post-HSCT relapse health states and across all model arms. It was assumed that no maintenance treatment was received following HSCT in a 2L line setting.

The distribution of subsequent treatments received 2L depended on the 1L treatment received and is summarised in Table 27. The differential distribution of 2L treatments was informed by clinical advice which suggested that patients would be more likely to receive gilteritinib (a 2nd generation FLT3i) when they hadn't received a 2nd generation FLT3i (i.e. midostaurin or SC) in the 1L setting. Consequently, the base case analysis assumes that fewer patients will receive 2L gilteritinib following quizartinib.

The mean time on subsequent treatment was sourced from the ADMIRAL trial which investigated the efficacy of gilteritinib vs. salvage chemotherapy in patients with relapsed or refractory *FLT3*+ AML. FLAG-Ida was one of the treatments offered to patients in the salvage chemotherapy arm of the trial. The median treatment duration of treatment of gilteritinib and salvage chemotherapy from ADMIRAL was applied in the model. The RDI of gilteritinib data from ADMIRAL and RDI for FLAG-Ida was assumed to be 100%. Wastage is accounted for 2L in the same way as in 1L.

Table 27 Dosing schedule, administration route, treatment distribution, mean time on treatment and RDI for the subsequent treatment regimens in the CEM (CS, Table 68)

	2L treatment distribution according to1L treatment choice[a]			Mean time on treatment (cycles)[b]	RDI[b]
	Quizartinib	SC	Midostaurin		
FLAG-Ida	60%	50%	40%	1.00	100%
Gilteritinib	40%	50%	60%	5.00	98%

Abbreviations: CEM: cost-effectiveness model; FLAG-Ida: fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor; G-CSF: granulocyte colony stimulating factor; IV: intravenous; 1L: first-line treatment; RDI: relative dose intensity; SC: standard chemotherapy.
References: Perl et al. 2019,[58] TA642[83]
Notes: Each cycle is 28 days in duration. a. treatment distribution is based on clinical expert opinion. b. Mean time on treatment for gilteritinib and FLAG-Ida therapy and RDI for gilteritinib were sourced from the ADMIRAL study. RDI for FLAG-Ida assumed.

EAG Comments

2L treatment not linked to effectiveness

As detailed in Table 27, transition probabilities applied in the Refractory, Relapse 1L, CR 2L health states are the same across all treatment regimens and based on pooled data from the ADMIRAL trial. This approach implicitly assumes that 50% of patients will receive salvage chemotherapy and 50% gilteritinib. This is inconsistent with the approach to modelling 2L drug acquisition costs and does not link costs with effectiveness. This is important because the base case analysis assumes a greater a proportion of patients will receive gilteritinib following SC and midostaurin and this not reflected in the applied transition probabilities. It also means that the higher drug acquisition costs associated with gilteritinib are not associated with any additional benefits which results in bias in favour of quizartinib. At the clarification stage (Question B15b), the EAG requested that the company update their analysis to link applied transition probabilities to the distribution of 2L treatments. Results of this scenario analysis are presented in Section 5.3.

The proportion of patients who receive subsequent treatment with gilteritinib

The EAG disagrees with that the distribution of subsequent treatments will depend on 1L treatment received and believes that the base case model underestimates the proportion of patients that will receive gilteritinib. Clinical advice received by the EAG indicates that that the vast majority (approx. 90%) of patients would receive gilteritinib in the 2L setting regardless of previous treatment received. Clinical advice to the EAG also indicates that *FLT3 TKD* mutations are frequently acquired at relapse and that gilteritinib is effective in patients with both *FLT3 TKD* and *FLT3 ITD* mutations. At the

clarification stage (Question B15c), the EAG requested that the company implement scenarios assuming 90% of patients receive subsequent gilteritinib in all refractory and relapsed patients. The results of this scenario analysis are presented in Section 5.3.

4.4.2.3 Allogenic haematopoietic stem cell transplant

The cost of HSCT was calculated as a weighted average of the cost of the different types of HSCT (in those 19 years or over) listed in the NHS reference costs (elective and non-elective inpatient costs were considered).[75] This cost (£39,257.06) was applied to all patients who received a transplant on entry to the first HSCT health state. HSCT is associated with a serious AE known as GVHD as described in CS, Section B.3.3.5 The associated costs per episode are calculated as £61,023.63.

4.4.2.4 Disease management and treatment monitoring costs

Disease management costs

Disease management costs were included in the model to account for the routine monitoring visits and procedures which occur during AML patient's treatment pathway (CS, Section B.3.5.5). These costs were calculated on a per-cycle basis for each health state. Unit costs were sourced from PPSRU 2022 report,[84] the National schedule of NHS costs - 2021/22,[75] the National Institute for Health and Care Research interactive costing tool[76] and NICE TA523 (adjusted for inflation).

Frequency of disease management were primarily informed by NICE TA399 and TA523 which identified these frequencies using a healthcare resource utilisation (HCRU) questionnaire for resource use.[21, 74] Assumptions were made to account for the additional health states used in the quizartinib model:

- Frequency of disease management resource use in the refractory health state was assumed to be equal to that of the relapsed state.
- Frequency of disease management resource use in the CR2, relapse2, HSCT treatment 2L and HSCT recovery 2L health states were assumed to be equal to their respective health state in the first line.

Treatment monitoring costs

The treatment monitoring unit costs are described in CS, Document B, Table 70. The frequencies of treatment monitoring usage are by treatment line (1L and 2L) sourced from NICE TA523[68] and TA399.[74] The frequencies are assumed to be the same across all treatment arms except for red blood cell transfusions and platelet transfusions in induction. These transfusions were sourced from the company IPD, with patients treated with midostaurin assumed to be the same. The 2L treatment monitoring frequencies were assumed to be the same across the treatment regimens for both the relapse and refractory health states. ECG monitoring costs were considered in the model only for

patients who initiate the quizartinib regimen. The frequency of which was sourced from the quizartinib SmPC.[79]

EAG comments

Treatment monitoring frequency is similar across all comparator arms with ECG monitoring higher with quizartinib with costs applied per cycle. For 1L treatment, based on TA523, these costs would only be accrued in the induction and CR health states. In contrast, for 2L treatment, these costs would only be accrued during refractory or relapse health states. The EAG considers that while it is acceptable to use treatment monitoring and disease management costs taken from previous related TAs, it would have been preferable to have used bespoke evidence based on NHS current practice.

4.4.2.5 Adverse events unit costs

The unit costs associated with AEs is provided in CS, Document B, Table 78 of CS and were sourced from the National schedule of NHS costs 2021/22.[75] The percentage of patients who experienced AEs for quizartinib and SC are from the QuANTUM-First trial and the Stone *et al*.[33] publication of the RATIFY trial for midostaurin (including also patients with *FLT3-TKD* mutation). The AE unit costs were multiplied by the percentage of patients who experienced each of the AEs to calculate a weighted average cost by treatment regimen. The AE cost is applied as a one-off cost in the first cycle of the model.

EAG comments

In general, midostaurin is calculated to have more frequent AEs than quizartinib. The exception is GVHD where 55.9% in the Quizartinib arm having GVHD post-HSCT compared to 47.3% in SC and 39.0% in midostaurin.

The EAG accepts the one-off cost simplifying assumption since estimating the exact timing of AEs is not possible for all comparators relevant to the decision problem.

4.4.2.6 Terminal care costs

The cost for terminal care was sourced from the PSSRU Unit Costs of Health and Social Care 2022 manual which estimated that the average cost of terminal care from death from any cause was £12,397.[84] This cost was applied as a one-off cost at the time of death irrespective of cause.

EAG comments

The EAG considers this value acceptable.

4.4.2.7 Confidential pricing arrangements

The EAG notes that there are a number of confidential commercial arrangements in place for drugs comprising the comparator regimen, and for drugs currently in use as subsequent treatment options.

The treatment acquisition costs used in the analyses presented in the company submission and the EAR (Section 6), include only the confidential pricing agreement for quizartinib.

Table 28 presents details of which comparator and subsequent treatments have confidential prices which differ from the publicly available list prices used to generate the results in this report. These prices were made available to the EAG and were used to replicate all analyses presented in the EAR for consideration by the Appraisal Committee. Details of all confidential pricing arrangements and all results inclusive of these arrangements are provided in the confidential appendix to this report. These prices were correct as of 12th March 2024.

Table 28 Source of the confidential prices used in the confidential appendix.

Treatment	Source of price/type of confidential arrangement
Quizartinib	Simple PAS/commercial access agreement
Midostaurin	Simple PAS/commercial access agreement
Idarubicin	eMIT price (two preparations available)
Cytarabine	eMIT price (five preparations available)
Fludarabine	eMIT price (two preparations available)
Filgrastim (G-CSF)	CMU (23 preparations available)
Gilteritinib	Simple PAS/commercial access agreement
Sorafenib	eMIT price

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The results of the company's revised base case following the clarification response are summarised in this section. The results in the following sections are inclusive of the PAS discounts for quizartinib unless stated otherwise. Results inclusive of available commercial arrangements for the comparator treatments are provided in a confidential appendix to the EAG report.

5.1.1 Deterministic Results

The company base case results are presented below, Table 29, in a fully incremental format. Results for the fully incremental comparison show that quizartinib is associated with increased costs (cost difference of [redacted] and improved QALYs (incremental QALYs of [redacted]) compared with midostaurin. The company's base case ICER comparing quizartinib with midostaurin is £3,459 per QALY gained.

Table 29 Revised company base case: fully incremental deterministic results (company clarification response, Table 19

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER (£/QALY)
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,175
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,459

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-years; SC, standard chemotherapy

Results for the pairwise comparison of quizartinib with SC in the company base case are also presented in Table 30. The results show that quizartinib is associated with increased costs (cost difference of [redacted] and improved QALYs (incremental QALYs of [redacted]) compared with SC. The company's base case ICER comparing quizartinib with SC is £17,364 per QALY gained.

Table 30 Revised company base case: pairwise comparison quizartinib vs SC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Quizartinib	[redacted]	[redacted]	[redacted]				
SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,364

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-years; SC, standard chemotherapy

5.1.2 Probabilistic Results

The EAG performed a probabilistic sensitivity analysis (PSA) on the revised company base case model, running 5,000 iterations for the fully incremental comparison. The mean probabilistic ICER for quizartinib compared to each of the comparators are presented below in Table 31. The PSA scatter plot, presented in Figure 9, shows that quizartinib is more effective and more costly compared to SC, and more effective with mixed results in costs in comparison to midostaurin. A multi-way cost-effectiveness acceptability curve for all three interventions is also shown in Figure 10.

Quizartinib has a [redacted] probability of being cost-effective at a threshold of £20,000 per QALY, and an [redacted] probability of being cost-effective at a threshold of £30,000 per QALY (Figure 10).

Table 31 Revised company base case results: fully incremental probabilistic analyses

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER (£/QALY)
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,523
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,858

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-years; SC, standard chemotherapy

Figure 9 Cost-effectiveness plane (generated from company model)

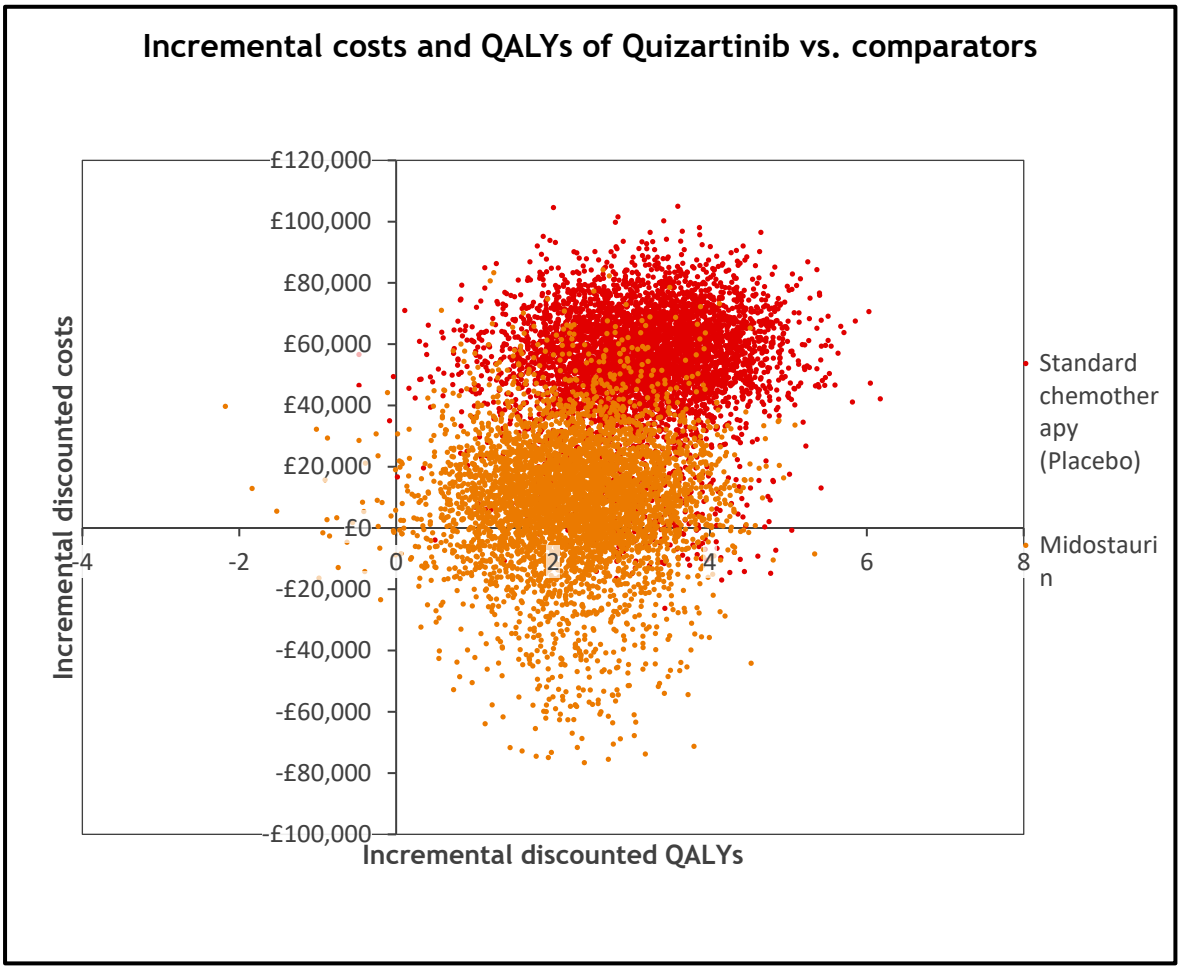


Figure 10 Multi-way cost-effectiveness acceptability curve (generated from company model)

5.2 Company's deterministic sensitivity analyses

The company conducted a series of one-way deterministic sensitivity analyses (DSAs) to identify variables with the greatest effects on the ICER for quizartinib compared to SC, and the net monetary benefit (NMB) for quizartinib compared to midostaurin. The DSA for the comparison between quizartinib and SC, presented in Figure 11, suggests that the relative treatment of SC in relapse after CRc, transition probabilities for SC from Induction 1 to refractory, and mean treatment duration on quizartinib maintenance were the most influential parameters on the ICER. For the comparison between quizartinib and midostaurin, presented in Figure 12, results suggest that relative treatment of midostaurin in relapse after CRc, the proportion using quizartinib maintenance post-HSCT, and relative dose intensity were the most influential parameters on the NMB.

Figure 11 Tornado diagram: quizartinib versus SC (generated from company model)

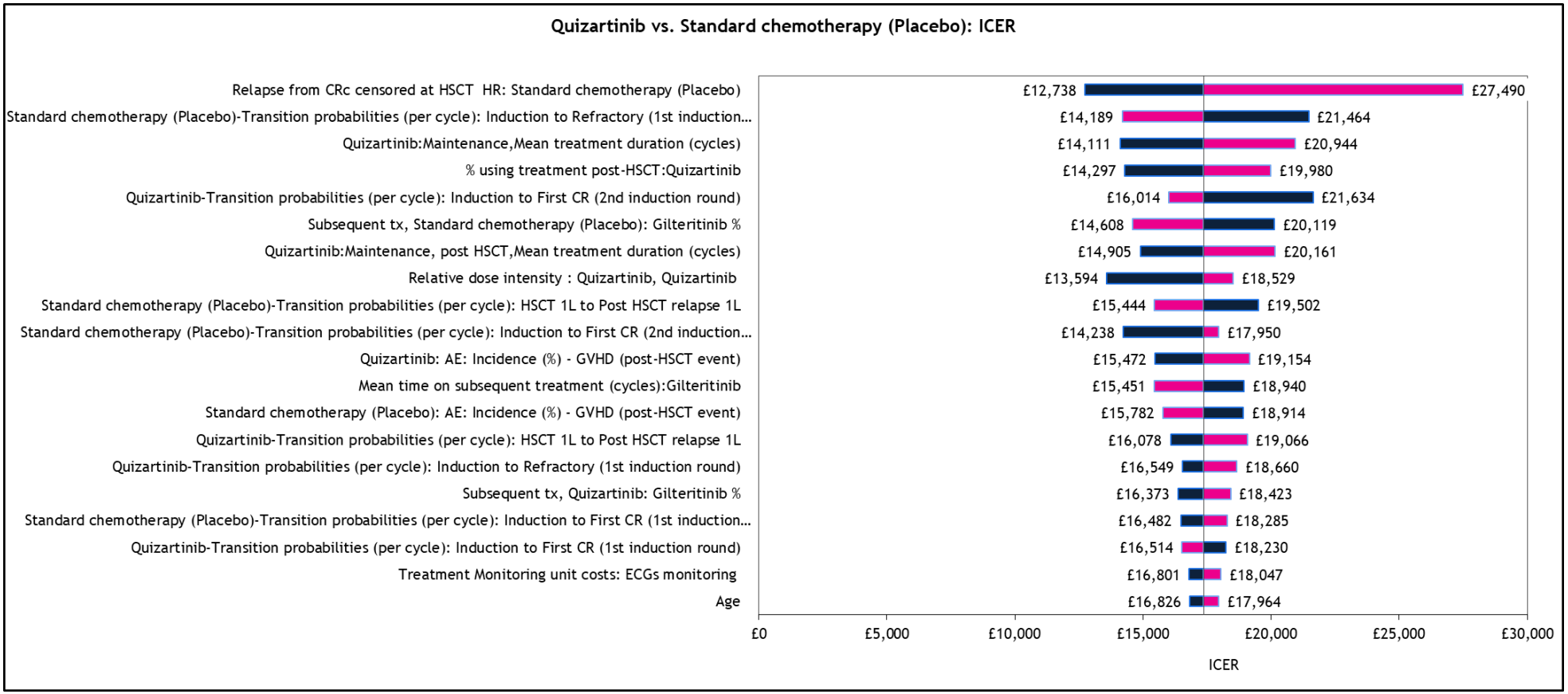
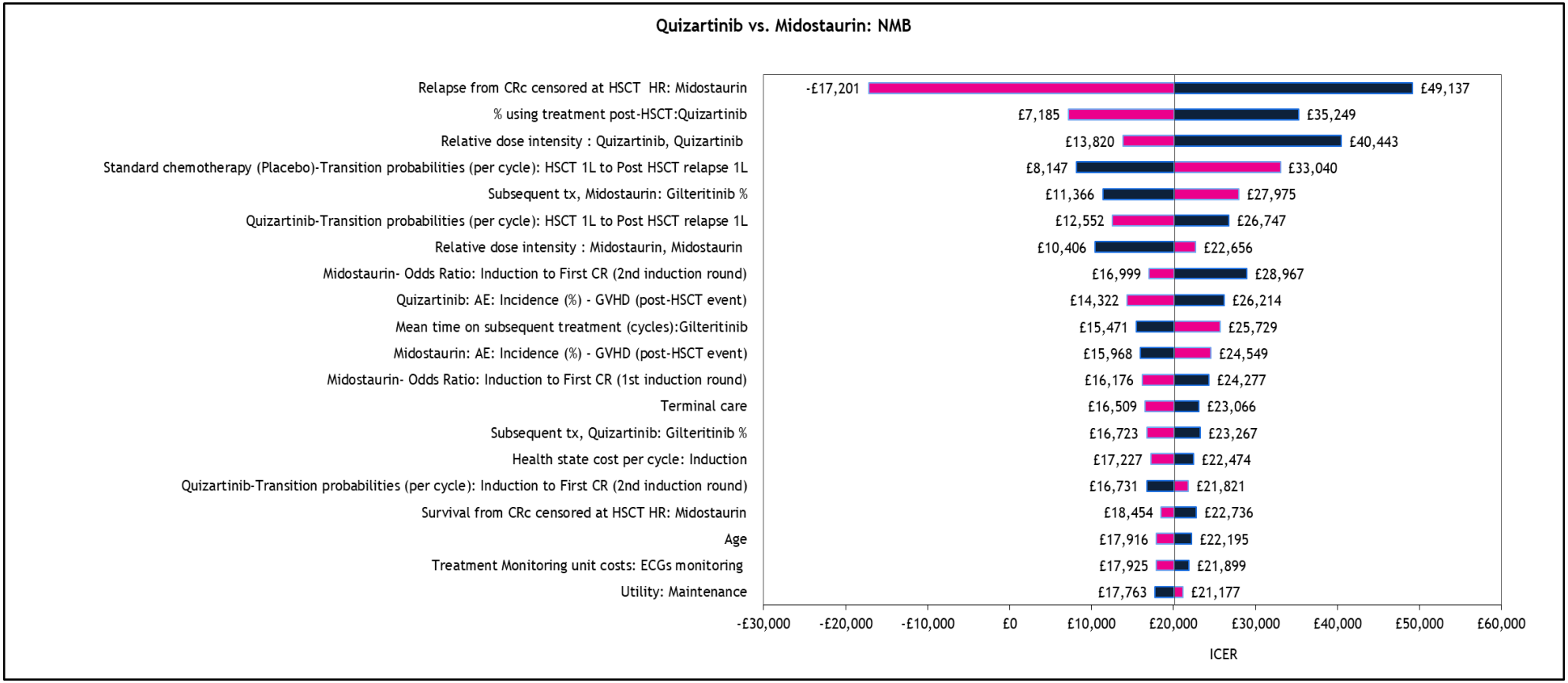


Figure 12 Tornado diagram: quizartinib versus midostaurin (generated from company model)



5.3 Company's additional scenario analyses

At the clarification stage, the EAG requested that the company present several scenario analyses to explore alternative assumptions and parameter inputs. The scenarios explored and the results of these analyses are presented in Table 32.

Table 32 Company's additional scenario analyses: fully incremental deterministic

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Fully incremental ICER (£/QALY)
i) Nested PSM used to model the effectiveness of 2L treatment (CQ B1c)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,994
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£311
ii) Nested PSM allowing cure in 2L (CQ B1b)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,478
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,773
iii) a) Modelling an alternative cure point at 2 years (CQ B4)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,529
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,385
b) Modelling an alternative cure point at 5 years (CQ B4)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,513
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,229
iv) Allowing transitions from CR 1L and HSCT 1L to relapse after achieving cure (CQ B4)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£112,711
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,597
v) Aligning transition probabilities in the 1st and 2nd induction with observed data in QuANTUM-First (CQ B5b)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,694
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,497
vi) Assuming the same risk death from CRc for quizartinib and midostaurin (HR=1) (CQ B7a)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,692
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,271
vii) Modelling OS using KM + survival curve and QuANTUM-First trial data for SC (CQ B7b)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,487

Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,589
viii) Applying time-varying transition probabilities for relapse after HSCT (CQ B8b)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,415
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,940
ix) Using EQ-5D data from the QuANTUM-First trial (CQ B11b)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,374
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,431
x) Modelling time on treatment based on observed QuANTUM-First data (CQ B12a)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,022
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,763
xi) Assuming the same proportion of patients receiving quizartinib and sorafenib post-HSCT maintenance (CQ B14)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,736
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,347
xii) Transition probabilities in refractory, relapse 1L and post-HSCT linked to subsequent treatment (CQ B15b)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,846
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,432
xiii) Assuming 90% of patients receive gilteritinib across all treatment arms* (CQ B15c)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,017
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,387
xiv) a) post-HSCT maintenance therapy with sorafenib applying unanchored MAIC results (HR=1.21 quizartinib vs sorafenib) (CQ B9)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,172
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,117
b) post-HSCT maintenance therapy with sorafenib assuming same efficacy (HR=1 quizartinib vs sorafenib) (CQ B9)							
SC regimen	[redacted]	[redacted]	[redacted]				
Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,487
Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,048

Abbreviations: 1L: first line; 2L: second line: CQ: clarification question; CR1: complete remission in first line; CRc: composite complete remission; HR: hazard ratio; HSCT: allogeneic haematopoietic stem cell transplant; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier LYG: life-years gained; OS: overall survival PSM: partitioned survival model; QALY: quality-adjusted life-years; SC: standard chemotherapy

*This scenario was modelled together with scenario xii

5.4 Model validation and face validity check

The company performed model validation in which the internal validity and face validity of the model was assessed. The internal validity check consisted of several quality control procedures, which model functionality, internal consistency, inputs and data reviewed by health economists. Model inputs and assumptions were also validated in consultations with clinical and HEOR experts. Face validity was assessed by comparing the model's predicted incremental QALYs for midostaurin compared to SC with those reported in a manufacturer sponsored cost-effectiveness analysis. This comparison suggests some disparity in results with the company's base case model predicting a QALY gain of 1.06 compared to 1.47 in the published analysis.

Validation undertaken by the EAG

As part of the EAG assessment of the economic analysis, the EAG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. Due to time constraints, the EAG's formal validation of the model focused on the PSM version of the economic model in which 2L treatment is modelled using a nested PSM model. Where errors were identified in the PSM version of the model the company's preferred version of model was also checked for the same errors.

Overall, the model was well coded, and the errors identified by the EAG largely minor. The EAG is however, concerned that a thorough validation of the economic model was not completed by the company as a large number of small errors were identified by the EAG, many of which were identified by the EAG following only rudimentary validity checks. All identified errors were corrected by the EAG, and a revised model supplied to the company with altered cells highlighted to aid verification. These corrections did not impact substantively on the model's predictions. Revised results are presented in Section 6.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified several limitations and areas of uncertainty in the company's cost-effectiveness analysis. These issues are identified and critiqued in Section 4.2. The EAG presents several alternative scenarios where an alternative approach was considered more appropriate, or where it was considered important to explore the impact of uncertainty. In response to the EAG's clarification questions, the company provided several scenario analyses, a few of which a reproduced in the EAG exploratory analyses. The EAG includes several further scenarios in the following section to demonstrate the impact of alternative assumptions on the EAG base case.

Descriptions of the exploratory analyses are presented in Section 6.1 and the impact of these analyses on the revised company's base case are presented in Section 6.2 and Section 6.3, along with the EAG's preferred base case.

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The following deterministic exploratory analyses were conducted by the EAG following corrections to the company's revised base case as described in Section 4, including the calculations of the proportion of patients entering the HSCT 1L state and HSCT 1L costs. Each of the following analyses are based on the company's revised and 'corrected' base case model and the nested PSM approach provided by the company in scenario analyses.

1. a. PSM structure

As described in Section 4.2.2, the EAG highlights issues with the company's approach to incorporating the effectiveness of 2L treatment. The company's approach is overly complicated and fails to capture the possibility of cure within 2L, limiting the model's ability to accurately reflect outcomes in the ADMIRAL trial informing outcomes in a 2L setting. The EAG proposed a simpler alternative approach to modelling 2L treatment and better reflects the underlying data.

b. Correction of calculations errors

This scenario corrects the calculation errors identified by the EAG.

c. PSM structure with 2L cure

As described in Section 4.2.2, the company's approach to modelling 2L relies on the assumption of time-invariant transition probabilities across the 2L health states. This fails to capture the possibility patients achieving cure in the 2L setting, contradicting the evidence from the ADMIRAL trial and committee discussion in TA 642. This scenario builds on scenario 1a by also allowing patients to

achieve in 2L setting. In line with the company base case assumptions cure is assumed after 3 years and move to general population mortality rates with a SMR of 2 applied.

d. EAG preferred specification of the PSM

This scenario revises the implementation of PSM in the following ways:

- Cure assumptions are applied to both the EFS and PD health state such that no further management costs are employed after the cure point and a utility value of 0.747 is applied to both health states.
- Time on treatment for gilteritinib is revised to 5 months and drug acquisition, administration and monitoring costs are applied as a lump sum in cycle 0.
- PSM is used to determine outcomes in patients who relapse following HSCT.

2. a. QuANTUM-First population

As discussed in Section 4.2.3, the EAG does not consider the RATIFY-like population reflective of clinical practice. Clinical advice to both the company and the EAG is that the QuANTUM-First ITT population is more representative than the RATIFY trial population of the NHS population who would be eligible for treatment with quizartinib. This scenario therefore revises the modelled population characteristics to align with the QuANTUM population. Most importantly, the mean age of the modelled cohort is increased from 47 to 54.

b. Induction reconfigured to better integrate relative effectiveness estimates

As described in Section 4.2.6.1, the induction health state is made up of two sub-tunnel health states: Induction 1 and Induction 2. This approach attempts to reflect the clinical reality of induction treatment phase but means that the relative treatment effects on CR cannot appropriately be integrated into the economic model and means that the OR generated from the MAIC of CR primarily drive the proportion of patients who move to a 2nd induction no the overall proportion who achieve CRc. In this scenario the EAG revises the calculations used in the induction health state, so it is better able to reflect the underlying trial data and also allows a more meaningful integration of the relative treatment effects generated by the indirect comparisons. The key difference between the company and EAG approach is that under the company approach the proportion of patients moving to 2nd induction is estimated as residual of other transition probabilities while the EAG approach assumes estimates the proportion of patients with refractory disease as a residual. Because data available to implement this scenario is only available for the QuANTUM-First population this scenario is applied together with scenario 2a.

c. Treatment effects drawn from the ML-NMR

This scenario is an extension of Scenario 3a and reflects the EAG's preference for using the unadjusted QuANTUM-First population to estimate treatment effectiveness. In this scenario the OR applied to the induction health state and HR applied to model relapse and death from CRc are derived from the ML-NMR rather the MAIC as preferred by the company.

d. Relapse and OS data for quizartinib based on QuANTUM-First trial

This scenario further builds on scenario and changes to directly use the QuANTUM-First trial data and includes a series of changes to the clinical data used in the model. This mitigates the issues associated with applying constant marginal HR where non-proportional hazards are present. It also removes the avoids the company base case assumption that OS from time of randomisation can suitably proxy for OS from CRc. The EAG considers this assumption to the clearly violated and to lack any clinical credibility. These changes are summarised in Table 33.

Table 33 Summary of changes made in scenario 3d

	Scenario 3c			Scenario 3d		
	Quizartinib	SC	Midostaurin	Quizartinib	SC	Midostaurin
Relaspe from CRc	ML-NMR HR applied to SC reference arm	Quantum first trial data	ML-NMR HR applied to SC reference arm	Quantum first trial data	Quantum first trial data	MLNMR HR applied to SC reference arm
Death from CRc	ML-NMR HR applied to SC reference arm	Quantum first trial data	MLNMR HR applied to SC reference arm	Quantum first trial data	Quantum first trial data	Assumed the same as quizartinib arm

Abbreviations: CRc: composite complete remission, HR: hazard ratio; ML-NMR: multilevel network meta-regression; SC: standard chemotherapy;

e. Treatment effects drawn from indirect comparison with AMLSG 16-10 trial

The EAG recognises limitations of the available evidence from the RATIFY trial to inform the comparisons between quizartinib and midostaurin. The AMLSG 15-10 trial provides alternative source of relative treatment effect allow some of the uncertainty associated with both MAIC and MLMNR to explored. This scenario utilises the EAG's direct comparison presented in Section 3.6.1.2 (Table 13) and revises the OR applied to the induction health state and the HR applied to model relapse from CRc.

f. 3c + preferred extrapolations

As explained in Section 4.2.6.2, the structural assumption of 'functional' cure applied at 3 years does not necessitate the need to extrapolate observed data as the duration of trial follow-up is beyond 3 years. The EAG proposes that the selection of survival curves is reflective of the proportion of

patients reaching the cure point in the observed data and demonstrate good visual fit of both the SC and quizartinib arms to the observed QuANTUM-First KM data. This scenario applies the EAG's preferred extrapolations to the unadjusted QuANTUM-First data, namely the generalised gamma for relapse from CRc and Gompertz for OS from CRc.

g. MAIC preferred extrapolations

Following the explanation above for EAG Scenario 3f. This scenario rests the model treatment effects to reflect the company base case assumptions and applies the EAG preferred extrapolations for relapse from CRc and OS from CRc, namely the generalised gamma for relapse from CRc and loglogistic for OS from CRc.

3. KM data for post-HSCT relapse

As highlighted in Section 4.2.6.3, the company employed an inconsistent approach to modelling transitions in the HSCT 1L health state. Time-invariant transition probabilities were used to model relapsed events while time-varying probabilities were used to model OS events in the company's base case model. This scenario revises the transition probabilities applied to model relapse from HSCT 1L so that they are informed time-varying transition probabilities.

4. QuANTUM-First HRQoL

As discussed in Section 4.3, the health state utility values applied in the company's base case are based on published values and do not incorporate the EQ-5D data collected in the QuANTUM-First trial. Following the EAG's request at clarification, the company provided a scenario analysis utilising the values generated from the QuANTUM-First trial to align with the NICE reference case. The EAG notes that the company provided limited detail on the methods used to generate the utility value set and whether the EQ-5D-5L values were mapped to EQ-5D-3L. This scenario utilises the observed trial utility values.

5. a. Linking treatment effect to second line therapy

As discussed in Section 4.2.6, transition probabilities from the refractory, relapse 1 and CR2 health states were informed by pooled data from the ADMIRAL trial. The company base case assumes a differing proportion of patients receiving FLAG-Ida and gilteritinib in 2L based on the treatment received in 1L, while assuming equal efficacy across all treatment arms. Following the EAG's request at clarification, the company provided a scenario analysis with transition probabilities applied in the refractory, relapse 1 and CR2 health states linked to percentage usage of subsequent treatments (FLAG-Ida and gilteritinib) at second line. This scenario is replicated in this section.

b. Assuming 90% of patients receive subsequent treatment with gilteritinib

As discussed in Section 4.4.2.2 the EAG considers that the base case model underestimates the proportion of patients that receive gilteritinib in clinical practice. Clinical advice to the EAG suggests that a vast majority (an estimated 90%) of refractory or relapse patients in the first-line setting would receive gilteritinib as second-line treatment. This is irrespective of the treatment option given in 1L. Following the EAG's request at clarification, the company provided a scenario analysis assuming 90% of patients will receive gilteritinib at second line across all treatment arms. This scenario is replicated in this section.

6. a. Exploring post-HSCT maintenance therapy with sorafenib following SC and midostaurin

The EAG raised concern over the exclusion of sorafenib as a key comparator in the post-HSCT maintenance therapy setting noting that it now represents standard care on the NHS. Following the EAG's clarification request, the company considered sorafenib in treatment sequences in this setting for both midostaurin and SC. This scenario models post-HSCT sorafenib maintenance therapy in the SC and midostaurin arms. The effectiveness of sorafenib is considered by assuming patients post HSCT survival is the same for both sorafenib and quizartinib.

These scenarios (6a-7b) assume the same proportion of patients ([redacted]) receive sorafenib maintenance treatment post-HSCT and quizartinib maintenance treatment post-HSCT based on QuANTUM-First data for quizartinib.

b. Effectiveness of sorafenib drawn from indirection comparison

As part of their clarification repose the company the company provided an unanchored MAIC comparing OS outcomes for quizartinib and sorafenib, using data from the QuANTUM-First and SORMAIN trials. This scenario builds on scenario 6a by revising post-HSCT outcomes in the SC and midostaurin arms by apply a HR [redacted]) drawn from this analysis.

7. a. Exploring post-HSCT maintenance therapy with sorafenib following quizartinib

This scenario further builds on scenario 6 and assumes that patients receiving quizartinib induction therapy will receive sorafenib as a post HSCT maintenance therapy. As per scenario 6a this scenario assumes that sorafenib and quizartinib of equivalent efficacy and that sorafenib is used following SC and midostaurin.

b. Effectiveness of sorafenib drawn from indirection comparison

This is equivalent to scenario 6b and models post-HSCT outcomes by applying the HR generated from the MAIC using the post-HSCT survival curve for quizartinib as a reference arm. As per 7a it assumed that patients will receive sorafenib as a post HSCT maintenance therapy regardless of the induction therapy received

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The results of the scenario analyses described in Section 6.1 are presented in Table 34. These results include the PAS discount for quizartinib only. Results inclusive of all available PAS discounts and other commercial arrangements are provided in the confidential appendix to this report.

Table 34 EAG Exploratory fully incremental scenario analyses (deterministic)

	Scenario	Technology	Total		Incremental		Fully incremental ICER
			Costs	QALYs	Costs	QALYs	
	Company base case	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£47,175
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,459
1a	**PSM structure**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,994
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£311
1b	**PSM structure + 2L cure**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,478
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,773
1c	**Calculation errors**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£23,526
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£18,000
2a	**QuANTUM-First population**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£55,937
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£4,220
2b	**2a + Induction reconfigured**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£61,324
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,843
2c	**2a + ML-NMR**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£140,509
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£4,272
2d	**2c+direct RFS and OS**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£176,732
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£6,083
2e	**2d+ AMLSG 16-10 trial of midostaurin**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£32,979
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2f		SC regimen	[redacted]	[redacted]			

	2d+ preferred extrapolations	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£166,361
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,792
2g	**MAIC preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£101,755
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,498
3	**KM data for post-HSCT relapse**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£47,415
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£2,940
4	**QuANTUM-First HRQoL**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£46,374
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,431
5a	**Linking treatment effect to 2nd line therapy**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£46,846
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,432
5b	**Assuming 90% of patients receive gilteritinib**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£40,787
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,352
5c	**5a+5b**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£41,017
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,387
6a	**Sorafenib maintenance (mido+SC) HR 1**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£30,431
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,347
6b	**Sorafenib maintenance (mido+SC) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£30,117
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,431
7a	**Sorafenib maintenance (all) HR 1**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£12,958
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7b	**Sorafenib maintenance (all) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,731
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: HR: hazard ratio; HRQoL: health-related quality of life; HSCT: allogeneic haematopoietic stem cell transplant; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; mido: midostaurin; ML-NMR: multilevel network meta-regression; OS: overall survival; PSM: partitioned survival model; QALY: quality-adjusted life-years; RFS: relapse-free survival; SC, standard chemotherapy; 2L: second line

The scenario analyses described in Section 6.1 are replicated in the PSM version of the company's base case model, as shown in Table 35. Note that Scenario 5a, and thus Scenario 5c, is only relevant to the non-PSM approach, hence they are not replicated in this section.

Table 35 EAG Exploratory fully incremental scenario analyses on PSM structure (deterministic)

	Scenario	Technology	Total	Incremental	

			Costs	QALYs	Costs	QALYs	Fully incremental ICER
	Company base case	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£47,175
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,459
1a	**PSM structure**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,994
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£311
1b	**PSM structure + calculation errors**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£53,263
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£862
1c	**PSM structure + Cure (PSM model)**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,478
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,773
1d	**EAG preferred configuration of PSM**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,914
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£5,229
2a	**QuANTUM-First population**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£62,772
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£537
2b	**2a + Induction reconfigured**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£20,281
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2c	**2a + ML-NMR**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£31,966
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2d	**2c+direct RFS and OS**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£277,872
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,059
2e	**2d+ AMLSG 16-10 trial of midostaurin**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£31,234
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
2f	**2d+ preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£251,788
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£3,975
2g	**MAIC preferred extrapolations**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£117,696
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£183
3	**KM data for post-HSCT relapse**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£16,363
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
4	**QuANTUM-First HRQoL**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,059

		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£309
5b	**Assuming 90% of patients receive gilteritinib**	SC regimen	[redacted]	[redacted]			
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£44,618
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£1,480
6a	**Sorafenib maintenance (mido+SC) HR 1**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,721
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
6b	**Sorafenib maintenance (mido+SC) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,965
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7a	**Sorafenib maintenance (all) HR 1**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£13,783
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
7b	**Sorafenib maintenance (all) HR [redacted] indirect**	SC regimen	[redacted]	[redacted]			
		Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£10,507
		Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: HR: hazard ratio; HRQoL: health-related quality of life; HSCT: allogeneic haematopoietic stem cell transplant; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; mido: midostaurin; ML-NMR: multilevel network meta-regression; OS: overall survival; PSM: partitioned survival model; QALY: quality-adjusted life-years; RFS: relapse-free survival; SC, standard chemotherapy; 2L: second line

6.3 EAG's preferred assumptions

Fully incremental results are of the EAG's preferred base case are presented in Table 36, and the pairwise comparison of quizartinib with SC in Table 37. Note that the results below are only inclusive of the PAS discount available for quizartinib. Results inclusive of all available commercial arrangements are presented in the confidential appendix to this report.

The EAG base case incorporates the following scenarios described in Section 6.1:

Scenario 1a: PSM structure

Scenario 1b: PSM structure + calculation errors

Scenario 1c: PSM structure + Cure

Scenario 1d: EAG preferred configuration of PSM

Scenario 2b: 2a + Induction reconfigured

Scenario 2f: 2d + preferred extrapolations

Scenario 3: KM data for post HSCT relapse

Scenario 4: QuANTUM-First HRQL

Scenario 5b: Assuming 90% of patients receive subsequent treatment with gilteritinib

Table 36 EAG's preferred base case (fully incremental deterministic results)

Scenario	Technology	Total		Incremental		Fully incremental ICER
		Costs	QALYs	Costs	QALYs	

EAG-corrected company base-case (PSM)	SC regimen	[redacted]	[redacted]			
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£133,861
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£17,288

Abbreviations: EAG: evidence assessment group; ICER: incremental cost-effectiveness ratio; PSM: partitioned survival model; QALY: quality-adjusted life-years

Table 37 EAG's preferred base case (pairwise deterministic results quizartinib vs SC)

Scenario	Technology	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
EAG-corrected company base-case (PSM)	Quizartinib	[redacted]	[redacted]			
	SC regimen	[redacted]	[redacted]	[redacted]	[redacted]	£52,519

Abbreviations: EAG: evidence assessment group; ICER: incremental cost-effectiveness ratio; PSM: partitioned survival model; QALY: quality-adjusted life-years

6.3.1 Summary of the company's cost-effectiveness analysis

The company submitted a *de novo* economic model to assess the cost-effectiveness of quizartinib for the treatment of patients with newly diagnosed with *FLT3-ITD*+ AML. The analysis compared a quizartinib based treatment regimen with established clinical management consisting of either a midostaurin based treatment regimen or standard chemotherapy (SC). In a pairwise comparison with SC the results of the company's base-case analysis that quizartinib is associated with increased costs (cost difference of [redacted]) but higher accrued QALYs (QALY difference of [redacted], with an ICER of [redacted] per QALY gained. In a pairwise comparison with midostaurin the results of the company's base-case analysis that quizartinib is associated with increased costs (cost difference of [redacted]) but higher accrued QALYs (QALY difference of [redacted], with an ICER of [redacted] per QALY gained.

In the company's probabilistic base-case analysis it was estimated that quizartinib has a [redacted] probability of being cost-effective at a threshold of £20,000 per QALY, and an [redacted] probability of being cost-effective at a threshold of £30,000 per QALY. Note that these results are based on the net price of quizartinib inclusive of a patient access scheme but are exclusive of confidential commercial arrangements for the comparator therapies.

6.3.2 Conclusions of the EAG's Critique

The economic analysis submitted by the company does not fully reflect the decision problem defined in the final scope, nor does it fully meet the requirements of the NICE reference case. The base case analysis presented by the company did not include sorafenib maintenance therapy, which represents standard care in the NHS for patients following HSCT. However, the scenario analysis presented by the company did explore the use of sorafenib in this setting. The utility set used in the company's base case was based on published values from the literature and did not use PRO data collected as part of

the QuANTUM-First trial. Furthermore, it is unclear whether the utility values provided at clarification have been appropriately mapped to EQ-5D-3L.

The EAG's review of company submission identified several areas of uncertainty, and a number of significant methodological issues which the EAG has sought to address where possible in the presented corrections and revised base case. The EAG's critique encompasses four broad themes: technical and consistency issues, model parametrisation, drivers of QALY gains, and the modelling of sorafenib.

The EAG identified numerous technical and consistency issues with the company's economic model and suggested several technical corrections. The most important of these pertains to the model structure, where the EAG recommended several changes to the company's base case model structure. These changes primarily concern the modelling of second line (2L) treatment, where the EAG suggests that a nested PSM would be a better approach than the state transition modelling adopted in the company's base case. The nested PSM offers several advantages, simplifying the model structure while allowing for better integration of the supporting data. Additionally, the EAG proposed changes to the model structure for induction treatment to better integrate the evidence of relative effectiveness between midostaurin and quizartinib.

Other technical changes suggested by the EAG include revisions to the modelling of relapse following HSCT, improvements to the extrapolation of observed survival data, updating the utility set to use PRO data from the QuANTUM-First trial, and correcting several calculation errors in the company's executable model.

Regarding the parametrization of the model, the EAG considers the company's decision to model a RATIFY-like population unjustifiable, given the clear limitations of the RATIFY trial and the weight of clinical advice suggesting that the QuANTUM-First trial is more reflective of the NHS population eligible for quizartinib. The EAG's preference for modelling a QuANTUM-First population means that the EAG also rejects the MAIC analysis used in the company's base case to model the relative effectiveness of quizartinib compared to both standard care (SC) and midostaurin. Instead, the EAG favours using the ML-NMR but considers the company's current approach to integrating evidence from both the MAIC and ML-NMR inappropriate, as it relies on the PH assumption, which demonstrably does not hold. Consequently, the relative treatment effects modelled in the company's base case analysis lack face validity and exaggerate the benefits of quizartinib relative to both SC and midostaurin.

The EAG also raised concerns about how drug acquisition costs were estimated in the model, particularly regarding how time on treatment data is integrated into the economic model. The EAG

considers the company's base case approach deeply flawed and is concerned that it significantly underestimates the time spent on maintenance treatment with quizartinib.

The large OS improvements predicted for quizartinib primarily result from modelled improvements in the rate of relapse following CRc. However, it is unclear whether these improvements will be observed in practice. Evidence on OS from the indirect treatment comparisons conducted by both the company and the EAG does not support the sizable OS gains predicted by the model, casting doubt on the validity of the model's predictions. The EAG highlights that the company's model structure relies on an unsubstantiated surrogate relationship between relapse from CRc and OS. Moreover, the modelled benefits are based on indirect treatment comparisons that not only consider different outcomes than those modelled in the economic analysis but are also subject to very high levels of uncertainty. As detailed in Section 3, the EAG has significant concerns regarding the plausibility of the effect estimates produced by the indirect comparisons and considers it unclear whether they are robust enough to inform decision-making.

As highlighted above, the EAG considers that the company's base case analysis does not comply with the NICE scope, as it does not consider sorafenib as a post-HSCT maintenance therapy. The company has sought to partially address this issue by presenting additional scenario analyses that attempt to model the impact of sorafenib maintenance treatment. However, the EAG has substantive concerns regarding the clinical evidence supporting these scenarios and considers there to be substantial uncertainty regarding the relative effectiveness of quizartinib and sorafenib in the post-HSCT setting. Moreover, the EAG believes that these scenarios fail to address more fundamental concerns regarding the clinical effectiveness of post-HSCT quizartinib maintenance therapy. There is limited evidence to support the clinical benefit of quizartinib in this setting, which must be weighed against the considerable acquisition costs of quizartinib.

7 SEVERITY MODIFIER

The company's revised base case model includes a QALY shortfall analysis, calculated by dividing the absolute QALY shortfall by the expected total QALYs for the general population. The expected total QALYs for the general population was based on the 2019-20 National life tables for England and Wales from the ONS.[85] The population EQ-5D-3L data adjusted by age and sex were derived from Health Survey from England (HSE) 2014, as recommended by the NICE DSU.[31]

The company reported that the expected total QALYs for the general population was 12.8 (CS, Table 81). However, owing to an error in the coding of the economic model, this was an underestimation of the true value and has been corrected by the EAG. Further, the DSU TSD 23: A Guide to Calculating

Severity Shortfall for NICE Evaluations was published in January 2024,[86] after the initial company submission. The EAG therefore also provides analyses, using the DSU calculator.

Corrected results of the company's QALY shortfall analysis is presented in Table 38, along with the values generated in the EAG preferred base case. The results of incorporating the expected total QALYs for the general population from the DSU calculator imply that the absolute QALY shortfall is above 12 and could be considered for 1.2 severity weight when using SC as the comparator. As midostaurin is the primary comparator, the EAG feels that a severity modifier of 1 is applicable. Where EAG base case assumptions are used, the absolute QALY shortfall falls below 12 in both comparisons to SC and midostaurin. This is mainly because a higher starting age is used in the model.

Table 38 Summary of QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY Shortfall
Revised company base case				
Midostaurin	16.69	[redacted]	10.94	0.66
SC	16.69	[redacted]	11.95	0.72
Revised company base case (DSU calculator)				
Midostaurin	16.80	[redacted]	11.05	0.66
SC	16.80	[redacted]	12.07	0.72
EAG base case				
Midostaurin	14.57	[redacted]	9.66	0.66
SC	14.57	[redacted]	9.98	0.68
EAG base case (DSU calculator)				
Midostaurin	14.70	[redacted]	9.79	0.67
SC	14.70	[redacted]	10.11	0.69

8 APPENDIX TABLES

8.1 Critique of search strategies

Table 39 EAG appraisal of evidence identification for the SLR clinical effectiveness evidence

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	Search strategies for the International Health Technology Assessment (INAHTA) database, trial registries and conference abstracts were missing from the submission but provided in the company response clarification question C3.
Were appropriate sources searched?	PARTLY	Primary studies were sought from key databases and sources of published and unpublished healthcare literature. But limited searching for previous systematic reviews and health technology assessments - databases containing non-Cochrane systematic reviews (e.g. Epistemonikos, KSR Evidence and DARE) were not searched and a limited range of HTA websites were searched.
Was the timespan of the searches appropriate?	PARTLY	Database inception to May 2023. The searches were not updated for the company submissions in March 2024 and April 2024. Conference abstracts in Embase were restricted to those published from 2020 to May 2023.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	*Population* (*FLT3* positive AML) AND *Intervention* (quizartinib) OR *Comparators* (midostaurin, gliteritinib, crenolanib, cytarabline, daunorubincin, idarubicin, mitoxantrone, etopside, amsacrine, fludarabine) AND *Study design* (RCTs, non-randomised studies, systematic reviews, NMAs). As several study designs were eligible, and the problems associated with identifying non-randomised studies,[87] a more comprehensive approach would have been to remove the study design part of the search strategy and to apply this restriction at the screening stage of the review.
Were appropriate search terms used?	PARTLY	**Database searches** Terms for one of the comparators (sorafenib) were missing from the database search strategies. In addition, azacitine and the brand name vyxeos (cytarabine and daunorubincin drug combination) were missing from the search strategies. Search terms for RCTs in MEDLINE and Embase were fairly comprehensive, however terms for systematic reviews were limited and the MeSH Network Meta-Analysis/ was missing from the strategies. A selection of terms for non-randomised study types were included in the MEDLINE and Embase strategies. However, as there is no dedicated database for non-randomised studies and these study types are difficult to identify comprehensively with a search strategy or search filter in databases of healthcare literature,[87] it is possible that non-randomised studies may have been missed. **Hand searching** The keyword searches for some resources did not include the UK spelling leukaemia and HTA resources were only searched with the abbreviation AML. (company response to the clarification question C3, Table 52)
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	NO	The searches of Embase and MEDLINE used a selection of study design search terms rather than validated study design search filters.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 40 EAG appraisal of evidence identification for the SLR of cost-effectiveness evidence

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Search strategies for the International Health Technology Assessment (INAHTA) database, NICE website and conference abstracts were missing from the submission but provided in the company response clarification question C3.
Were appropriate sources searched?	PARTLY	The main databases searched were appropriate. Supplementary searching of HTA agency websites was limited to the NICE website only.
Was the timespan of the searches appropriate?	PARTLY	• Main databases - 2012 to May 2023. • Conference abstracts in Embase were restricted to those published from 2020 to May 2023. • NICE website and the INAHTA database were searched on 11th August 2023. • The searches were not updated for the March 2024 or the April 2024 company submissions.
Were appropriate parts of the PICOS included in the search strategies?	YES	*Population* (*FLT3*+ AML) AND *Study design* (economic evaluations). It was inappropriate to limit the searches of NHS EED, by study design. Population terms only should have been used to search this database.
Were appropriate search terms used?	PARTLY	Search terms for the population and study design were appropriate and comprehensive in most databases and resources searched. Keyword searches for some resources did not include the UK spelling leukaemia and HTA resources were only searched with the abbreviation AML (company response to the clarification question C3, Table 52)
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	NO	A very comprehensive set of search terms (both text word and subject headings) for economic evaluations were included in the search strategies for MEDLINE and Embase. The EAG therefore has no concerns that validated search filters were not used.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 41 EAG appraisal of evidence identification for the SLR of HRQoL evidence

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Search strategies for the International Health Technology Assessment (INAHTA) database, NICE website and conference abstracts were missing from the submission but provided in the company response to clarification question C3.
Were appropriate sources searched?	PARTLY	The main databases searched were appropriate. Supplementary searching of HTA agency websites was limited to the NICE website only.
Was the timespan of the searches appropriate?	PARTLY	• Main databases - database inception to May 2023. • Conference abstracts in Embase were restricted to those published from 2020 to May 2023. • NICE website and the INAHTA database were searched on 11th August 2023. • The searches were not updated for the March 2024 or the April 2024 company submissions.
Were appropriate parts of the PICOS included in the search strategies?	YES	*Population* (*FLT3*+ AML) AND *Outcomes* (utilities OR disutilities OR HRQoL).
Were appropriate search terms used?	PARTLY	Search terms for the population and outcomes were appropriate and comprehensive in most databases and resources searched. Keyword searches for some resources did not include the UK spelling leukaemia and HTA resources were only searched with the abbreviation AML (company response to clarification question C3, Table 52)
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	NO	Study design search filters were not utilised to restrict retrieval to utility/disutility/HRQoL studies. However, as a comprehensive range of terms to cover this concept were included in the strategies, along with named utility measures relevant to the population, the EAG has no concerns that validated search filters were not used.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Table 42 EAG appraisal of evidence identification for the SLR of healthcare cost and resource use evidence

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	YES	Search strategies for the International Health Technology Assessment (INAHTA) database, NICE website and conference abstracts were missing from the submission but provided in the company response to clarification question C3
Were appropriate sources searched?	PARTLY	The main databases searched were appropriate. Supplementary searching of HTA agency websites was limited to the NICE website only.
Was the timespan of the searches appropriate?	PARTLY	• Main databases - inception to May 2023. • Conference abstracts in Embase were restricted to those published from 2020 to May 2023. • NICE website and the INAHTA database were searched on 11th August 2023. • The searches were not updated for the March 2024 or the April 2024 company submissions.
Were appropriate parts of the PICOS included in the search strategies?	YES	*Population* (FLT3+ AML) AND *Study design* (costs OR resource use). It was inappropriate to limit the searches of NHS EED, by study design. Population terms only should have been used to search this database.
Were appropriate search terms used?	YES	Search terms for the population and outcomes were appropriate and comprehensive in most databases and resources searched. Keyword searches for some resources did not include the UK spelling leukaemia and HTA resources were only searched with the abbreviation AML (company response to clarification question C3, Table 52)
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	NO	A very comprehensive set of search terms (both text word and subject headings) for cost and resource use were included in the search strategies. The EAG therefore has no concerns that validated search filters were not used.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

8.2 Baseline characteristics in QuANTUM-First and RATIFY

Table 43. Baseline characteristics for the QuANTUM-First and RATIFY trials

	QuANTUM-FIRST *FLT3-ITD* **(ITT)**		**RATIFY** *FLT3-ITD*[a]	
	Quizartinib (N=268)	**Placebo** (N=271)	**Midostaurin** (N=230)	**Placebo** (N=222)
Age in years				
Median (Range)	56 (23, 75)	56 (20, 75)	47 (19, 59)	48 (18, 60)
Categorical Age, n (%)				
< 60	161 (60.1)	162 (59.8)	230 (100)	222 (100)
≥ 60, <65	37 (13.8)	44 (16.2)	Not eligible	Not eligible
≥ 65	70 (26.1)	65 (24.0)	Not eligible	Not eligible
Sex, n (%)				
Male	124 (46.3)	121 (44.6)	114 (49.6)	92 (41.4)
BMI (kg/m^2)				
N	[redacted]	[redacted]	NR	NR
Mean (SD)	[redacted]	[redacted]	NR	NR
Race, n (%)				
White	159 (59.3)	163 (60.1)	NR	NR
Asian	80 (29.9)	78 (28.8)	NR	NR
Black/African American	2 (0.7)	5 (1.8)	NR	NR
American Indian/Alaskan	0	1 (0.4)	NR	NR
Other	27 (10.1)	24 (8.9)	NR	NR
Ethnicity, n(%)				
Hispanic/Latino	[redacted]	[redacted]	NR	NR
Non-Hispanic/Non-Latino	[redacted]	[redacted]	NR	NR
Not reported	[redacted]	[redacted]	NR	NR
Region, n (%)				
North America	16 (6.0)	18 (6.6)	NR	NR
Europe	163 (60.8)	163 (60.1)	NR	NR
Asia/Other Regions	89 (33.2)	90 (33.2)	NR	NR
ECOG PS, n (%)				
0	87 (32.5)	98 (36.2)	NR	NR
1	134 (50.0)	136 (50.2)	NR	NR
2	47 (17.5)	36 (13.3)	NR	NR
Missing	[redacted]	[redacted]	NR	NR
Subtype of *FLT3*-ITD mutation, n(%)[b]				
FLT3-ITD with low allelic ratio (<0.5)	[redacted]	[redacted]	80 (34.8)	81 (36.6)
FLT3-ITD with high allelic ratio (> 0.5)	[redacted]	[redacted]	149 (65.2)	141 (63.4)

2017 ELN risk group, %[c]				
Favourable	NR	NR	25.2[e]	32.3 [e]
Intermediate	NR	NR	33.3 [e]	37.6 [e]
Adverse	NR	NR	41.5 [e]	30.1 [e]
Risk status with specific cytogenetic patterns, n(%)[d]				
Favourable	14 (5.2)	19 (7.0)	NR	NR
Intermediate	197 (73.5)	193 (71.2)	NR	NR
Adverse	19 (7.1)	27 (10.0)	NR	NR
Unknown	38 (14.2)	31 (11.4)[f]	NR	NR
Missing	0	1 (0.4)	NR	NR
Karyotype, n(%)				
Normal	NR	NR	107 (62.2)[e]	141 (80.1) [e]
Abnormal	NR	NR	65 (37.8) [e]	35 (19.9) [e]
NPM1 Mutation				
n (%)	142 (53.0)	140 (51.7)	95 (50.0) [e]	108 (64.3) [e]
Platelet counts 10^3µL				
Median (range)	[redacted]	[redacted]	NR	NR
ANC per mm^3				
Median (range)	[redacted]	[redacted]	NR	NR
WBC count at diagnosis of AML, n (%)				
< 4.0 × 10^9/L , n (%)	135 (50.4)	137 (50.6)	NA	NA
≥ 4.0 × 10^9/L, n (%)	133 (49.6)	134 (49.4)	NA	NA
Median (range), 10^9/L	NA	NA	42.6 (0.8, 304)	42.1 (0.8, 329.8)
Median bone marrow blast count				
n (Range)	[redacted]	[redacted]	77 (3, 100)	80 (6, 100)
Choice of anthracycline, n (%)				
Daunorubicin	[redacted]	[redacted]	NR	NR
Daunorubicin (C2), idarubicin (C1)	[redacted]	[redacted]	NR	NR
Idarubicin	[redacted]	[redacted]	NR	NR
Missing	[redacted]	[redacted]	NR	NR

Abbreviations: ANC: absolute neutrophil count; AML: acute myeloid leukaemia; C1: cycle 1; C2: cycle 2; ELN, European LeukemiaNet; FLT3: FMS-like tyrosine kinase 3; ITD: internal tandem duplication; ITT: intent-to-treat, NA: not applicable; NR: not reported; *NPM1:* nucleophosmin 1; WBC: white blood cell.

[a] Baseline characteristics for RATIFY's *FLT3-ITD* subgroup retrieved from Rücker et al[36]. Selected by means of available next-generation sequencing samples, the analysed study population covered a sample of 81% of FLT3-ITD+ patient population in RATIFY, which a clinical expert indicated is likely representative of the entire *FLT3-ITD+* patient population in RATIFY.

[b] The *FLT3* subtype of one patient (0.4%) in the quizartinib group was unknown/could not be determined.

[c] 2017 ELN guidelines stratified risk according to the genetic abnormality (including *FLT3*) identified at screening and categorised it into three groups: favourable, intermediate and adverse. Favourable: t(8;21)(q22;q22.1); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB MYH11, mutated NPM1 without FLT3-ITD or with FLT3-ITDlow, biallelic mutated CEBPA; intermediate: mutated NPM1 and *FLT3*-ITDhigh, wild-type NPM1 without *FLT3*-ITD or with *FLT3*-ITDlow (without adverse-risk genetic lesions), t(9;11)(p21.3;q23.3); MLLT3-KMT2A, cytogenetic abnormalities not classified as favourable or adverse; adverse: t(6;9)(p23;q34.1); DEK-NUP214, t(v;11q23.3); KMT2A rearranged,

t(9;22)(q34.1;q11.2); BCR ABL1, inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1), −5 or del(5q); −7; −17/abn(17p), complex karyotype, monosomal karyotype, wild-type NPM1 and FLT3-ITDhigh, mutated RUNX1, mutated ASXL1, mutated TP53.

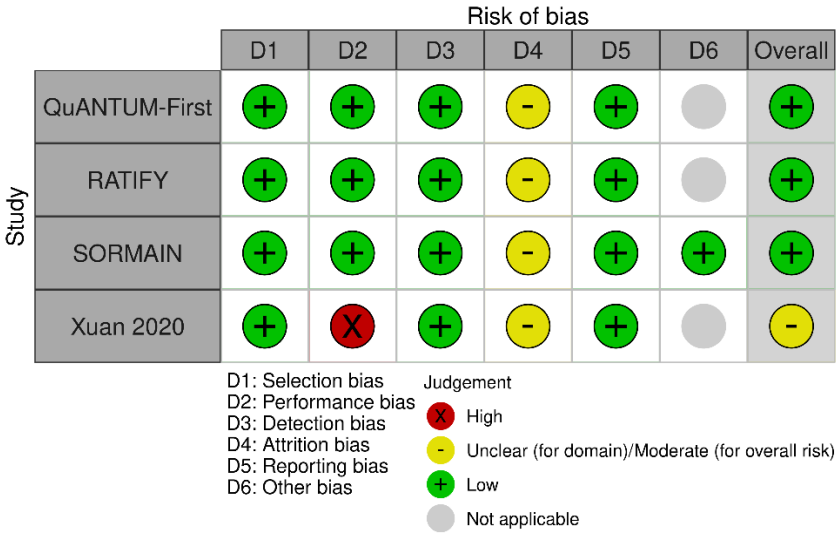
[d] Favourable: inv(16), t(16;16), t(8;21), t(15;17); intermediate: normal, +8, +6, -y; unfavourable: deI5q, -5, del7q, -7, complex.

[e] Data was not available for the full sample in these instances: 1. 2017 ELN risk group, midostaurin arm sample size: 135; placebo arm sample size: 133. 2. Karyotype, midostaurin arm sample size: 172; placebo arm sample size:176. 3. NPM1 mutation, midostaurin arm sample size: 190; placebo arm: 168.

[f] Number corrected from CS based on data from the CSR.

8.3 EAG risk of bias assessments

Table 44 Risk of bias assessment of RCTs considered for the indirect treatment comparison

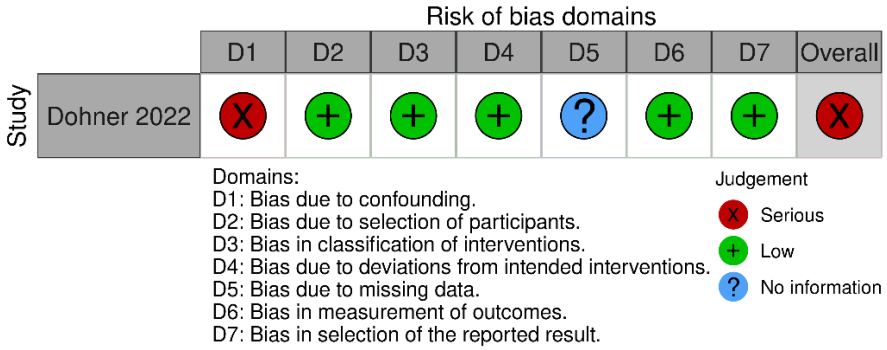


Justifications for unclear/high risk of bias judgments:

D2: In Xuan (2020), study personnel and participants were aware of the treatment received, which may have affected management decisions and biased OS comparisons between midostaurin and placebo.

D4: For all studies, there was insufficient information to assess whether results were robust to the presence of missing data.

Table 45 Risk of bias assessment of Dohner et al. (2022)



Justifications for serious concerns/no information judgments:

D1: Appropriate methods adjusted for a number of important variables including FLT3-ITD mutation. However, differences in management between the trial and the historical cohort from a heterogenous group of trials between 1993 and 2009, and against the older RATIFY trial, could not be adjusted for and may be significant.

D5: No evidence of whether results were robust to the presence of missing data.

Note: Risk of bias assessments were performed separately for comparisons between AMSLG 16-10 vs. historical cohorts, and between AMSLG 16-10 vs. RATIFY placebo arm. The results presented here apply to both comparisons.

8.4 Summary of adverse events in QuANTUM-First

Table 46 Summary of adverse events in QuANTUM-First

	Induction Phase, n (%)		Consolidation Phase, n (%)		Maintenance Phase, n (%)		Overall, n (%)	
	Quizartinib (N= 265)	**Placebo** (N = 268)	**Quizartinib** (N = 173)	**Placebo** (N = 175)	**Quizartinib** (N= 116)	**Placebo** (N= 92)	**Quizartinib** (N= 265)	**Placebo** (N = 268)
Patients with ≥ 1 TEAE	260 (98.1)	261 (97.4)	160 (92.5)	160 (91.4)	109 (94.0)	84 (91.3)	264 (99.6)	265 (98.9)
Grade ≥ 3	187 (70.6)	200 (74.6)	120 (69.4)	121 (69.1)	91 (78.4)	53 (57.6)	244 (92.1)	240 (89.6)
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with death as an outcome	19 (7.2)	13 (4.9)	8 (4.6)	5 (2.9)	3 (2.6)	7 (7.6)	30 (11.3)	26 (9.7)
Associated with drug discontinuation	26 (9.8)	11 (4.1)	10 (5.8)	5 (2.9)	18 (15.5)	7 (7.6)	54 (20.4)	23 (8.6)
Associated with drug dose interruption	24 (9.1)	30 (11.2)	14 (8.1)	13 (7.4)	65 (56.0)	22 (23.9)	90 (34.0)	54 (20.1)
Associated with drug dose reduction	7 (2.6)	3 (1.1)	4 (2.3)	0	42 (36.2)	14 (15.2)	50 (18.9)	17 (6.3)
Patients with ≥ 1 study-drug-related TEAE*	102 (38.5)	77 (28.7)	50 (28.9)	48 (27.4)	85 (73.3)	34 (37.0)	160 (60.4)[a]	97 (36.2)
Grade ≥ 3	56 (21.1)	43 (16.0)	34 (19.7)	26 (14.9)	62 (53.4)	16 (17.4)	118 (44.5)	65 (24.3)
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with death as an outcome	2 (0.8)	1 (0.4)	2 (1.2)	2 (1.1)	0	0	4 (1.5)	4 (1.5)
Associated with drug discontinuation	7 (2.6)	2 (0.7)	4 (2.3)	2 (1.1)	12 (10.3)	3 (3.3)	23 (8.7)	7 (2.6)
Associated with drug dose interruption	8 (3.0)	14 (5.2)	6 (3.5)	5 (2.9)	46 (39.7)	11 (12.0)	57 (21.5)	25 (9.3)
Associated with drug dose reduction	3 (1.1)	1 (0.4)	2 (1.2)	0	32 (27.6)	8 (8.7)	35 (13.2)	9 (3.4)
SAEs	75 (28.3)	66 (24.6)	59 (34.1)	54 (30.9)	39 (33.6)	34 (37.0)	143 (54)	123 (46)
Grade ≥ 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with death as an outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30 (11.3)	26 (9.7)
Associated with drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with drug dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with drug dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study-drug related SAEs*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥ 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with death as an outcome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with drug dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated with drug dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company submission, Document B, Tables 34-40 and QuANTUM-First CSR, Table 14.3.1.1.

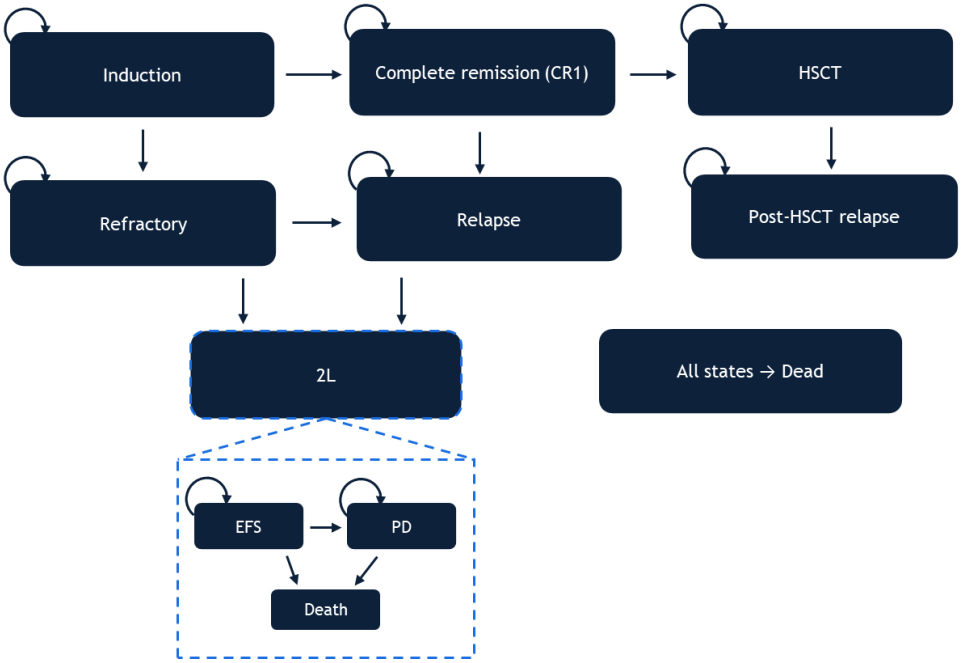
Abbreviations: SAE, severe adverse event; TEAE, treatment-emergent adverse event.

[a] Causality assessed by the investigator. [b] Reported as 161 (60.8) in the CSR. [c] Reported as 24 (9.0) in the CSR

8.5 PSM model

The nested PSM presented by the company in their clarification response comprised three mutually exclusive health states: (i) EFS, (ii) post-progression or progressive disease (PD), and (iii) death, which is the absorbing state. As depicted in Figure 13 patients with refractory and relapsed disease are assumed to enter a new health state: 2L where the PSM determines outcomes. The PSM therefore replaces the Refractory, Relapse 1L, CR2, HSCT 2L, HSCT recovery 2L, post-HSCT maintenance 2L and relapse 2L health states used in the company's base case model structure. A time horizon to death in the PSM was applied. Costs and benefits were discounted at 3.5% in line with the reference case. [60]

Figure 13: Model Structure (response to clarification question B1c, Figure 41)



Inputs and assumptions for 2L nested PSM

EFS and OS curves

To inform the 2L PSM model (and survival for patients entering 2L), it was necessary for the company to reconstruct and extrapolate EFS and OS curves from the ADMIRAL trial. With justification provided (BIC and AIC scores; generalised gamma distribution), blended survival curves were applied in the CEM (weighted by the proportion of patients receiving each subsequent treatment and adjusted for general population mortality) for quizartinib, SC, and midostaurin.

Health-related quality-of-life

To estimate the QALY pay-off for patients entering the 2L health state in the CEM, utilities were assigned to the EFS and PD health state. A utility value of 0.747 (CR2 utility value in the original

model) was applied to the EFS state. In the PD health state, a utility value of 0,477 was applied (Relapse 2 in the original model). The application of a cure assumption (implemented in scenario analysis) did not impact on the utility values applied. This contrasts with the approach used to model 1L treatment where utilities were assumed to be the same as those of the general population after the cure point.

Costs

Costs applied in the PSM included drug acquisition and administration costs, HSCT procedure costs, monitoring costs and disease management costs. Unit costs were primarily informed by NHS Reference Costs 2021-202,[77] and the BNF[78] and informed by assumptions adopted in the original model. The costs applied are summarised in Table 47.

Table 47 Summary of per cycle costs applied in the PSM

	Gilteritinib	**FLAG-IDA**
Drug acquisition costs	£13,968	£1,917
Administration costs	£0	£1,768
Monitoring costs	£,2,996	£0
Disease management costs	£457- EFS health state, £2,389-PD health state	
HSCT costs	£39,257	

In the gilteritinib arm duration of treatment was based on state occupancy with drug acquisition, administration (£0) and monitoring costs applied while patients were in the EFS health state. In the FLAG-IDA arm duration of treatment was assumed to be 1 cycle. HSCT costs were applied to 26% of patients in the gilteritinib arm and 15% in the FLAG-ID arm. This was informed by observed HSCT rates in the ADMIRAL trial.

8.5.1 EAG comment

8.5.1.1 Duration of treatment

The EAG considers the company's approach to modelling the duration of treatment in the gilteritinib arm to be unreasonable, as it is likely to result in excessive drug acquisition and monitoring costs. The EAG highlights that this approach differs from the one adopted in the original base case model structure where a mean treatment duration of 5 cycles is assumed. The EAG prefers to use the company’s original approach as its better accounts for cessation of treatment following HSCT aligning with the NICE recommendations. It also better aligns with data from the ADMIRAL trial where the median duration of treatment was 18 weeks.[58]

8.5.1.2 Application of the cure assumption

In their clarification response, the company included a scenario where cure is allowed in the 2L setting. This represents the EAG's preferred approach to modelling 2L treatment. However, the EAG considers this scenario to be specified, as the cure assumption is applied only to the EFS health state. This results in some patients remaining in the PD health state for the entire model time horizon, which is clinically unrealistic. This issue arises because the PSM uses a simplified approach that does not account for third-line therapy. While the EAG considers this approach reasonable, the company should have aligned with the assumptions accepted in TA523, where cure was also applied to surviving patients with relapsed disease (i.e. also applied to the PD health state).

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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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Note on the text

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

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.

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External Assessment Group Report
Quizartinib for untreated FLT3-ITD-positive acute myeloid leukaemia

EAG addendum: Additional analysis requested following the Pre-meeting briefing

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Note on the text

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

Copyright statement

1 OVERVIEW

Following the pre-meeting briefing (PMB) for appraisal committee 1 (ACM1) the Committee lead team requested the following additional analysis:

- A scenario analysis assuming the sane relapse rate for quizartinib and midostaurin
- A scenario assuming the clinical equivalence of quizartinib and midostaurin.

The NICE team further requested the following additional information:

- A comparison of drug acquisition costs for a full course of treatment with quizartinib and midostaurin
- A comparison of annualised drug acquisition costs associated with quizartinib and midostaurin.

2 RESULTS OF ADDITIONAL SCENARIO ANALYSIS

Table 1 presents the results of the additional scenario analysis requested by the Committee lead team. These analyses are run on the EAG's updated base case as outlined in the addendum on time on treatment. The scenarios set the efficacy of midostaurin equal to that of quizartinib. Therefore, the total QALYs and costs associated with quizartinib remain unchanged in these scenarios. The EAG considers this approach more appropriate to setting quizartinib equal to midostaurin as the principal uncertainty relates to the relative effectiveness of midostaurin. This also maintains consistency in the estimated cost-effectiveness of quizartinib vs standard chemotherapy.

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.

Table 1 Additional scenario analysis assuming equivalence between quizartinib and midostaurin

Scenario	Technology	Total		Incremental		Fully incremental ICER
		Costs	QALYs	Costs	QALYs	
Updated EAG base case inclusive of EAG preferred approach to ToT	SC regimen	[redacted]	[redacted]			
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£163,476
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£12,863
Equivalent rate of relapse for midostaurin and quizaertinib	SC regimen	[redacted]	[redacted]			
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£103,773
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£14,050
Clinical equivalence of midostaurin and quizaertinib	SC regimen	[redacted]	[redacted]			
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£48,566
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

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

2.1 EAG comment

The EAG urges caution when interpreting the equal efficacy scenarios and presents these for illustrative purposes only. There is limited clinical evidence supporting the equivalence of quizartinib and midostaurin. Results from the indirect treatment comparison are subject to considerable uncertainty. As discussed extensively in the evidence assessment report, there are significant methodological challenges with generating unbiased estimates of relevant treatment effect parameters due to the substantial differences between the RATIFY and QuANTUM First trials. Moreover, even if the results of the indirect treatment comparisons are taken at face value, the point estimates generated are associated with wide confidence intervals for all outcome measures.

It is also important to emphasise that the equal efficiency scenarios make several assumptions. Firstly, it assumes quizartinib is received in the post-HSCT setting for up to three years but is associated with no additional benefit. Secondly, patients on quizartinib receive maintenance treatment without HSCT for much longer than those on midostaurin, and this is also assumed to be associated with no benefit. It is unclear whether these assumptions are reasonable. The available evidence does not allow efficacy to be compared across treatment phases, and it is unclear whether maintenance therapy with either quizartinib or midostaurin offers any additional benefit.

3 ADDITIONAL INFORMATION ON DRUG ACQUISITION COSTS

Error! Reference source not found. presents a comparison of drug acquisition costs associated with quizartinib and midostaurin treatment regimens. The full course of treatment for quizartinib assumes two cycles of induction treatment, four cycles of consolidation treatment and 36 cycles of maintenance treatment. The full course of treatment for midostaurin assumes two cycles of induction treatment, four cycles of consolidation and 12 cycles of maintenance treatment. The annualised costs are presented based on 12 cycles of maintenance treatment.

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.

Table 2 Comparison of drug acquisition costs

Scenario	Technology	Undiscounted costs
Cost of a full course of treatment	Midostaurin regimen	£171,518
	Quizartinib regimen	[redacted]
Cost of 12 cycles of maintenance treatment	Midostaurin regimen	£134,639
	Quizartinib regimen	[redacted]

Single Technology Appraisal

Quizartinib for induction, consolidation and maintenance treatment of newly diagnosed FLT3-ITD-positive acute myeloid leukaemia [ID4042]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 21 June 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

1. Additional errors identified by the EAG

Following the submission of the Evidence Assessment Report (EAR), the Evidence Assessment Group (EAG) identified several errors that were not identified by the company during the factual accuracy check (FAC). The errors are as follows:

1. Scenario 2b, which reconfigures the induction health states, was implemented incorrectly. Consequently, the results reported for this scenario in Tables 1, 2, 34, and 35 of the EAR are incorrect.
2. Scenario 2b was wrongly excluded from the EAG base case when it should have been included. Therefore, the EAG base case results reported in Tables 36 and 37 of the EAR are incorrect.
3. The estimates of expected total QALYs for the general population, as reported in the company submission, were found to be incorrect. As a result, the estimates of absolute and proportional QALY shortfall reported in Table 38 are also incorrect.

The post-FAC EAR addresses these errors, as well as the factual inaccuracies identified by the company in their FAC submission.

2. Company Factual accuracy check

Issue 1 Modelling patients who relapse following HSCT to receive 2L treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, table for issue 7 "The EAG is also unclear why the company has neglected to model second-line salvage therapy in a post-HSCT relapse setting and considers this an important limitation of the company's base case model structure."	"~~The EAG is also unclear why the company has neglected to model second-line salvage therapy in a post-HSCT relapse setting and considers this an important limitation of the company's base case model structure~~ [Suggest deleting sentence]	In the company model, patients who relapse following HSCT are allowed to receive second-line (2L) treatment, and the subsequent treatment costs are included. However, patients in post-HSCT relapse who receive subsequent treatment are not considered for a second HSCT, as validated by	The EAG can confirm that 2L treatment costs were applied. We have reworded this section to focus on the modelling of outcomes which differs from the approach adopted in patients who relapse without HSCT. The EAG considers the PSM the most appropriate approach

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		UK clinical experts that patients are very unlikely to have a second HSCT. Additionally, patients in HSCT 1L relapse who receive subsequent treatment are also not allowed to transition to CR2 due to a lack of data to inform the transition. Introducing additional assumptions would increase the complexity and uncertainty of the model. Thus, the company suggests removing this statement	to modelling outcomes in patients who relapse following HSCT.
Page 96, Section 4.2.2. Model structure - modelling of 2L subsection. The wording of the following sentence does not accurately capture the true nature of the company's model structure: “Thirdly, the model structure does not allow patients who	Thirdly, the model structure **~~does not~~** allow**s** patients who relapse following HSCT to receive 2L treatment **by only taking into account the subsequent treatment costs in the post-HSCT Relapse heath state**.	Same as above	Text is similarly amended to focus on the approach to modelling outcomes. See response to previous comment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
relapse following HSCT to receive 2L treatment.”			

Issue 2 Approach on modelling time to treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment

The EAG recommends separate modelling approaches for time on treatment across the induction, consolidation, and maintenance phases. However, the EAG was unable to implement its recommended approach due to a lack of access to all the necessary data and concluded that the company's approach tends to underestimate the ICERs. The EAG called the company to action with the description of their intended method. The company conducted an exploratory analysis by applying the EAG's suggested approach to the EAG-preferred base case and found that it had a minimal impact on the ICER. Therefore, the company suggests updating the associated statements in the EAG report to reflect this limited impact. The	Insert new scenario on EAG PSM base case. Insert description of result of requested exploratory analysis.	The company considers the approach applied in its base case to be appropriate; however, additional exploratory analyses implementing EAG's preferred approach (EAR page 123 Table 26) to modelling time on treatment have been conducted to explore the uncertainty. These exploratory analyses were directly conducted based on the EAG model and its preferred base case. In summary: • All patients in 1st and 2nd induction cycles accrue 1 and 2 cycles • Consolidation costs are applied as a lump sum for all patients entering CR • Proportion of patients accruing maintenance treatment costs (with and without HSCT) is based on the respective K-M curves using the unadjusted QuANTUM-First population • Midostaurin for non-HSCT patients follows same curve as quizartinib, truncated at 12 months Both scenarios, with or without the RDI updated to a phased-based approach in the quizartinib arm, have been conducted.	Not a factual error. We appreciate the efforts taken to implement this analysis, but we cannot account for this in our report as it did not form part of the company submission or clarification response. We have, however, notify the NICE team and will consider this updated scenario in an addendum to our report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
relevant texts are listed in the rows below.		The exploratory analysis results showed that after implementing EAG's preferred approach to modelling time on treatment, including an adjustment of RDI, the ICERs decreased compared with the EAG-preferred base (results shown in Table 1 below).	
Page 22, table for issue 9 "The EAG considers that the company's approach to integrating the time on treatment evidence is very likely to underestimate the drug acquisition costs associated with quizartinib, particularly in the maintenance setting. The ICERs in the company's analysis are therefore likely to be underestimates."	The EAG considers that the company's approach to integrating the time on treatment evidence is very likely to underestimate the drug acquisition costs associated with quizartinib, particularly in the maintenance setting. The ICERs in the company's analysis are therefore likely to be underestimates. **An additional exploratory analysis has been conducted by the company, which implemented the EAG-preferred approach on**	An additional exploratory analysis has been conducted to implement the EAG-preferred approach on modelling time to treatment, as described above. The results show that the ICERs in the company's base case were overestimated. Therefore, we suggest updating the information in the EAG report.	Not a factual error. See previous response.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	modeling time to treatment. The results show that this alternative approach to modeling time to treatment is consistent in result with the company approach.		
Page 149, Section 6.3.2. "The EAG also raised concerns about how drug acquisition costs were estimated in the model, particularly regarding how time on treatment data is integrated into the economic model. The EAG considers the company's base case approach deeply flawed and is concerned that it significantly underestimates the time spent on maintenance treatment with quizartinib."	The EAG also raised concerns about how drug acquisition costs were estimated in the model, particularly regarding how time on treatment data is integrated into the economic model. ~~The EAG considers the company's base case approach deeply flawed and is concerned that it significantly underestimates the time spent on maintenance treatment with quizartinib.~~ **An additional exploratory analysis has been conducted by the**	Same as above	Not a factual error. See previous response.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	company, which implemented the EAG-preferred approach on modeling time to treatment. The results show that this alternative approach to modeling time to treatment is consistent in result with the company approach.		

Table 1. Results of exploratory analysis implementing EAG's preferred approach to modelling time on treatment

Scenario	Technology	Total		Incremental		Fully incremental ICER
		Costs	QALYs	Costs	QALYs	
EAG-corrected company base-case (PSM)	SC regimen	[redacted]	[redacted]	-	-	-
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£157,362
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£21,762
Exploratory analysis a: EAG-corrected company base-case (PSM) + EAG preferred approach to modelling time on treatment, without the RDI updated to a phased-based approach in the quizartinib arm	SC regimen	[redacted]	[redacted]	-	-	-
	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£186,883
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£23,242
	SC regimen	[redacted]	[redacted]	-	-	-

Exploratory analysis b: EAG-corrected company base-case (PSM) + EAG preferred approach to modelling time on treatment, with the RDI updated to a phased-based approach in the quizartinib arm	Midostaurin regimen	[redacted]	[redacted]	[redacted]	[redacted]	£186,883
	Quizartinib regimen	[redacted]	[redacted]	[redacted]	[redacted]	£15,436

Issue 3 Calculation for transition to HSCT/Calculation errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has used a different approach for calculating the transition to HSCT 1L in the economic evaluation. However, this alternative approach seems to be referenced by the EAG as a calculation error. The company would like this to be clarified in the EAG report. The relevant texts are listed in the rows below.	N/A	In the company base case, the model was developed to transition all patients to HSCT in cycle 4. This assumption was based on the QuANTUM-First study, where HSCT was performed in CR1 after a median time of 3.5 months (equivalent to 3.8 model cycles) in the quizartinib arm and 3.3 months (equivalent to 3.5 model cycles) in the placebo arm. However, based on the changes made by the EAG in the model, it transitioned patients from CR to HSCT as soon as they achieved CR. This implies that patients could receive HSCT from cycle 2, which is earlier than the evidence from the QuANTUM-First study. These changes were noted as "calculation errors" in the EAG report. However, the company	Not a factual error. The EAG considers the company's base case assumption that HSCT is received in cycle 4 conceptually reasonable, aligning with both practice and the QuANTUM-First trial. The changes applied by the EAG, however, reflect that the fact that the model was original base-case was underestimating the proportion of patients that proceed to HSCT. This occurred because of relapse and death events occurring prior to cycle 4. The EAG corrections ensure that the correct proportion of patients receive HSCT.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		believes this should be considered an alternative approach to calculate the transition to HSCT with different assumptions than the company's base case, instead of “errors.” Thus, the company suggests clarifying this in the EAG report.	
Page 137, section 5.4: “The EAG is however, concerned that a thorough validation of the economic model was not completed by the company as a large number of small errors were identified by the EAG, many of which were identified by the EAG following only rudimentary validity checks.”	~~The EAG is however, concerned that a thorough validation of the economic model was not completed by the company as a large number of small errors were identified by the EAG, many of which were identified by the EAG following only rudimentary validity checks.~~ [Suggest deleting sentence]	The company has reviewed the calculation errors identified by the EAG in the model and found that most of the 'errors' were actually an alternative approach for modelling the transition to HSCT as mentioned above. Only one error was found to be associated with the company’s base case (i.e., a formula error in cell N588 in the 'Inputs' worksheet), which has a minor impact on the ICER vs. SC (company-submitted revised base case: £17,374/QALY gained; error corrected: £17,351/QALY gained), while	Not a factual error. The EAG has consistently found errors in the company model at all stages of the NICE process.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		the ICER vs. midostaurin remained unchanged. Other errors were irrelevant to the company's base case and were associated with scenarios used to explore uncertainty. The relevant aspects are detailed below: • 2L PSM scenario • Sorafenib drug acquisition costs • Sensitivity on the number of induction cycles Therefore, the company suggests removing this sentence, as it is misleading. It is important that confidence in the company ICER is not unfairly undermined by suggestion of a large number of calculation errors.	
Page 138, section 6.1	This scenario **performs an alternative approach to model the transition to HSCT and** corrects a minor coding error~~s~~* identified by the EAG.	As mentioned above, the new method of modelling the transition to HSCT should be	Not a factual error. See previous responses.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td>“This scenario corrects the calculation errors identified by the EAG.”</td><td><u>*One formula error was identified in the company submitted base case in cell N588 in the 'Inputs' worksheet. This error leads the ICER vs. SC to be overestimated (company-submitted revised base case: £17,374/QALY gained; error corrected: £17,351/QALY gained), while the ICER vs. midostaurin remained unchanged.</u></td><td>considered as a new approach with different assumptions than the company’s base case, rather than as calculation errors.

Therefore, the company suggests clarifying this and adding a footnote to detail the calculation error identified in the model for transparency.</td><td></td></tr>
<tr><td>Page 24, Table 1 and

Page 143, Table 34

<table><tr><td>1c</td><td>Calculation errors</td></tr></table></td><td><table><tr><td>1c</td><td><u>Alternative approach in modeling transition to HSCT + Minor coding</u> error<u>*</u></td></tr></table>
<u>*One formular error was identified in the company submitted base case in cell N588 in the 'Inputs' worksheet. This error leads the ICER vs. SC to be overestimated (company-submitted revised base case: £17,374/QALY gained; error corrected: £17,351/QALY gained), while the ICER vs. midostaurin remained unchanged.</u></td><td>As mentioned above, the new method of modelling the transition to HSCT should be considered as a new approach with different assumptions than the company’s base case, rather than as calculation errors.

The increase in the ICER in this scenario compared to the base case is mostly related to the alternative approach for modelling the transition to HSCT.

Therefore, the company suggests clarifying this, and</td><td>Not a factual error. See previous responses.</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		ideally separate this out, in the report and adding a footnote to detail the calculation error identified in the model for transparency.	
Page 25, Table 2 and Page 145, Table 35 1b: PSM structure + calculation errors	1b: PSM structure + **alternative approach in modeling transition to HSCT** + minor coding error***** ***One formular error was identified in the company submitted base case in cell N588 in the 'Inputs' worksheet. This error leads the ICER vs. SC to be overestimated (company-submitted revised base case: £17,374/QALY gained; error corrected: £17,351/QALY gained), while the ICER vs. midostaurin remained unchanged. In addition, the EAG corrected the formula errors in the 2L PSM scenario, including correcting the formulas in cells AZ9, BP9, and CF9 in the "2L-PSM" worksheet and the formulas in column AC in the "LYs" worksheet.**	Same as above	Not a factual error. See previous responses.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 27, section 1.5 and Page 146, section 6.3 "Scenario 1b: PSM structure + calculation errors"	"Scenario 1b: PSM structure + **alternative approach in modeling transition to HSCT** + minor coding error~~s~~*" ***One formula error was identified in the company submitted base case in cell N588 in the 'Inputs' worksheet. This error leads the ICER vs. SC to be overestimated (company-submitted revised base case: £17,374/QALY gained; error corrected: £17,351/QALY gained), while the ICER vs. midostaurin remained unchanged.**	Same as above	Not a factual error. See previous responses.

Issue 4 Minor wording/data corrections for accuracy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Cumulative Incidence of Relapse (CIR) HR (95% CI) is not accurately presented in: • Page 46, table 5: • Page 54, section 3.2.4.3	[redacted]	Minor wording changes to ensure the information presented is accurate.	The EAG believes these values are correct and refer to the values for CIR (not RFS) provided by the company in their

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td></td><td></td><td>response to clarification (question A5).</td></tr>
<tr><td>Page 99, section 4.2.4.1:
“Quizartinib is administered on days 8–21 of the induction and consolidation phases.”</td><td>Quizartinib is administered on days 8–21 of the induction and <u>on days 6-19 of the</u> consolidation phase<s>s</s>.</td><td>Minor wording changes to ensure the information presented is accurate.</td><td>Amended as suggested</td></tr>
<tr><td>Page 110, section 4.2.6.3.
“The company however conducted a scenario analysis with the post-HSCT survival for midostaurin set equal to the quizartinib arm.”</td><td>The company however conducted a scenario analysis <u>considering sorafenib as the post-HSCT maintenance treatment in the midostaurin arm</u>, with the post-HSCT survival for <s>midostaurin</s> <u>sorafenib</u> set equal to the quizartinib arm.</td><td>Minor wording changes to ensure the information presented is accurate.</td><td>Amended as suggested</td></tr>
<tr><td>Page 111, section 4.2.6.4
The assumptions listed in the Table 21 are inaccurately states.</td><td><table>
<tr><th>Transition from:</th><th>Assumptions</th></tr>
<tr><td>Relapse 1L</td><td><u>i)</u> The same TPs applied to all regimens for transition <u>from Relapse 1L to CR 2L</u>.
<u>ii) The same TP applied to midostaurin and quizartinib</u></td></tr>
<tr><td>CR 2L</td><td><s>None</s> <u>The same TPs applied to all regimens.</u></td></tr>
<tr><td>Relapse 2L</td><td><s>i)</s> Assumed the same as the transition probability from Relapse 1L to Death.</td></tr>
</table></td><td>Minor wording changes to ensure the information presented is accurate.</td><td>Amended as suggested</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	~~**ii) The same TPs applied to all regimens.**~~		
Page 115, section 4.3.2: • [redacted] • [redacted] • [redacted] • [redacted]	Page 115, section 4.3.2: • [redacted] • [redacted] • [redacted] • [redacted]	Minor wording changes to ensure the information presented is accurate.	Amended as suggested
Page 120, section 4.4.2.1 "A patient access scheme (PAS) is available for quizartinib consisting of a simple discount of [redacted]"	"A patient access scheme (PAS) is available for quizartinib consisting of a simple discount of [redacted]"	Minor wording changes to ensure the information presented is accurate.	Amended as suggested
Page 125, section 4.4.2.4 "Frequency of disease management resource use in the CR2, relapse2, HSCT treatment 2L and HSCT recovery 2L health states were assumed to be equal to the HSCT 1L health state."	"Frequency of disease management resource use in the CR2, relapse2, HSCT treatment 2L and HSCT recovery 2L health states were assumed to be equal to ~~the HSCT~~ **their respective** ~~1L~~ health state **in the first line**."	Minor wording changes to ensure the information presented is accurate.	Amended as suggested
Page 147, section 6.3.1: "In a pairwise comparison with midostaurin the results of the company's base-case analysis that quizartinib is	~~"In a pairwise comparison with midostaurin the results of the company's base-case analysis that quizartinib is associated with increased costs (cost difference of [redacted]) but higher accrued~~	The presented sentence is duplicated.	Values have been corrected to reflect the pairwise comparisons of quizartinib with SC and with midostaurin

<table>
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<tr><td>associated with increased costs (cost difference of [redacted]) but higher accrued QALYs (QALY difference of [redacted], with an ICER of [redacted] per QALY gained.”</td><td><s>QALYs (QALY difference of [redacted], with an ICER of [redacted] per QALY gained.”</s>

[Delete sentence]</td><td></td><td></td></tr>
<tr><td>There are some discrepancies identified in the figures in Table 46, page 159, in section 8.4, Summary of Adverse Events in QuANTUM-First.</td><td>The table below indicates the figures which should be used for the respective cells in Table 46.
<table>
<tr><td></td><td colspan="2">Overall</td></tr>
<tr><td></td><td>Quizartinib</td><td>Placebo</td></tr>
<tr><td colspan="3">SAEs</td></tr>
<tr><td>Grade ≥ 3</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Grade 3</td><td>[redacted]</td><td>No change</td></tr>
<tr><td>Grade 4</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Associated with drug discontinuation</td><td>[redacted]</td><td>No change</td></tr>
<tr><td colspan="3">Study drug related SAEs</td></tr>
<tr><td>Associated with drug dose reduction</td><td>[redacted]</td><td>No change</td></tr>
</table></td><td>Proposed updates are in line with data in the CSR Appendix Table 14.3.1.1</td><td>Amended as suggested</td></tr>
</table>