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

Technology appraisal committee C (6 August 2024)

Confidential information redacted

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Background on acute myeloid leukaemia

Rapidly progressing cancer, more common in older people

Symptoms and prognosis

- Acute myeloid leukaemia (AML) is a rapidly progressing cancer of the blood and bone marrow
- Symptoms include fatigue, fever, infections, bruising, memory loss, pain, nausea and vomiting

Epidemiology

- Incidence rate of AML in UK 2016-18 was 4.7 cases per 100,000 persons
- Over 70% of new cases are in people over 60 years of age
- The 5-year net survival for acute myeloid leukaemia is around 13.6%

Diagnosis and classification

- Around 27% of cases in the UK have the FLT3-ITD mutation (subset of FLT3 mutation)
    - Associated with poor prognosis, increased risk of relapse and shorter survival, compared with FLT3-TKD positive disease

Abbreviations: FLT3-ITD, Feline McDonough sarcoma-like tyrosine kinase 3 internal tandem duplication

Patient perspectives

Unmet need for new treatments

Submissions from Blood Cancer UK and Leukaemia Care

- Because the disease progresses so quickly, treatment starts so quickly that patients have no chance to prepare, causing shock and fear
- Symptoms include fatigue, pain, breathlessness, memory loss, bleeding and bruising, itching, nausea and vomiting
    - Can lead to difficulties moving around, performing daily tasks and taking care of themselves
- Most people spend months in hospital having intensive treatments with debilitating side effects e.g. rashes, diarrhoea, mouth ulcers, incontinence, heart damage
- Repeated infections can quickly become life-threatening
- No current treatments that specifically target FLT3-ITD mutation
- In the maintenance treatment setting, unlike oral azacitidine and midostaurin, quizartinib can be used after stem cell transplant.

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.

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.

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Abbreviations: AML, acute myeloid leukaemia; FLT3-ITD, Feline McDonough sarcoma-like tyrosine kinase 3 internal tandem duplication

Clinical perspectives

Survival benefit appears promising, but some elements remain unclear

Submission from Royal College of Pathologists

- Treatment pathway is well-defined for people with FLT3 positive AML (midostaurin + daunorubicin + cytarabine), but is more contentious when there is overlapping diagnostic and clinicopathological information, for example people with both a FLT3 variant and a history of myelodysplastic syndrome (MDS), or MDS-related cytogenetic abnormalities
- Maintenance with quizartinib can be resumed following HSCT unlike in current NHS practice, where midostaurin or oral azacitidine may not routinely be used in the post-transplant setting
- The number of cycles of maintenance therapy is 36 with quizartinib compared to 12 cycles of midostaurin – so additional monitoring will be required (ECG and blood count monitoring)
- Quizartinib offers an alternative option to patients who may be intolerant of current care
- Unclear if quizartinib surpasses midostaurin benefits without head-to-head comparison
- The role of maintenance therapy with both inhibitors and impact on quality of life remain unclear
- In subgroups of older patients in QuANTUM-First (60-64 and ≥65), difference in efficacy between quizartinib and placebo was not statistically significant

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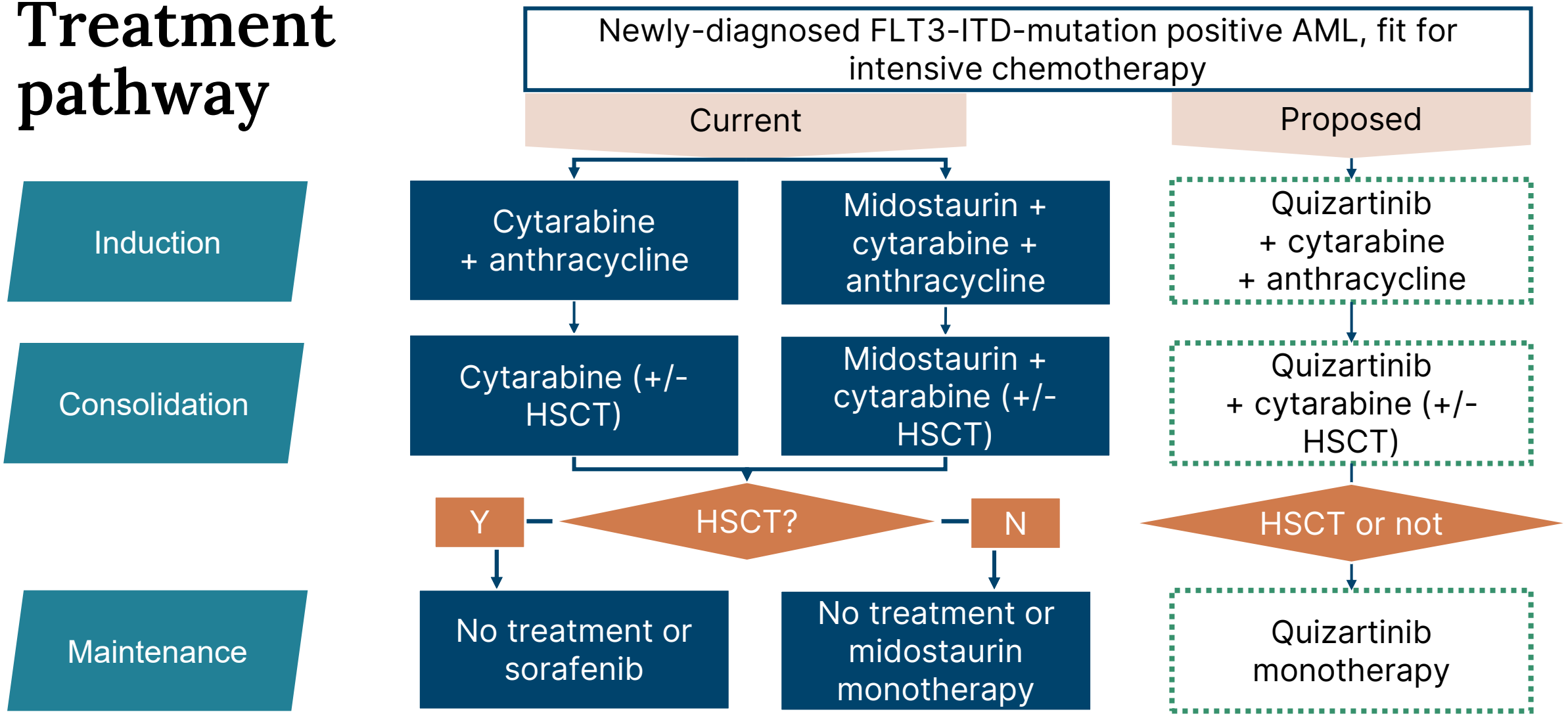
Abbreviations: AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase 3; SCT, stem cell transplant; ECG, electrocardiogram

Equality considerations

- One stakeholder highlighted that midostaurin appeared to be associated with a survival improvement in males but not females (RATIFY subgroup), but quizartinib may favour survival in females (QuANTUM-First subgroup).
    - Stakeholder stated that the amount and quality of data are insufficient for this to be a consideration at present
- At scoping, a stakeholder noted that while the clinical trial was conducted in ages 18-75, NICE guidance should cover all adults for equality purposes
    - NICE will appraise quizartinib in line with the marketing authorisation, which does not have an upper age limit

Treatment pathway



EAG considers that standard chemotherapy alone is rarely used in practice and a midostaurin-based regimen is the main comparator

Is standard chemotherapy alone a relevant comparator?

Abbreviations: AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell transplant; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication

Quizartinib (Vanflyta, Daiichi Sankyo)

Marketing authorisation	• GB marketing authorisation granted March 2024 • 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+.
Mechanism of action	• Tyrosine kinase FLT3 inhibitor
Administration	Oral tablets
Price	• 20mg quizartinib dihydrochloride x 28 tablets: [redacted] • 30mg quizartinib dihydrochloride x 56 tablets: [redacted] • The average modelled cost of a course of treatment is [redacted](company base case) • All figures here are at list price - a PAS discount has been approved

Abbreviations: EMA, European Medicines Agency; AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; PAS, patient access scheme

Key issues (1)

Key:
Large Small Unknown

Key issue	Questions for consideration	ICER impact
1) Comparators	Is standard chemotherapy alone a relevant comparator?	Large
2) Indirect treatment comparisons	Is there robust evidence of improved efficacy compared with midostaurin for overall survival, complete remission or cumulative incidence of relapse? a. Is it appropriate to compare QuANTUM-First and RATIFY in an indirect treatment comparison? b. Are the results of the MAICs and ML-NMR appropriate for decision-making? c. Are the results of the ITCs applied correctly in the economic model?	Unknown
3) Economic model results	Is the economic model suitable for decision making? Are the results of the model valid, given the clinical evidence available? a. Should the RATIFY-like population or QuANTUM-First population be the modelled population? b. Should the company's or EAG's approach to modelling induction state be used? c. Is the company approach or EAG approach more reliable for the transitions from the complete remission health state?	Large

Abbreviations: MAIC, matched-adjusted indirect treatment comparison; ML-NMR, multilevel network meta-regression; HSCT, hematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; CR, complete remission; 1L, first-line; KM, Kaplan-Meier

Key issues (2)

Key:
Large Small Unknown

Key issues	Questions for consultation	ICER impact
4) Maintenance phase	a. Should sorafenib be included as a comparator in the post-HSCT maintenance phase? b. Is the company's unanchored MAIC suitable for decision-making?	Unknown
5) Post-HSCT treatment effectiveness	Should the transition from HSCT 1L to relapse in the model be based on time invariant probabilities from QuANTUM-First, or KM data from QuANTUM-First?	Small
6) Second-line treatment modelling	a. Should second-line treatment be modelled using a state transition or partitioned survival model? b. Should cure be possible after second-line treatment? c. Should remission after HSCT relapse be possible in the model? d. What proportion of people are likely to have gilteritinib as subsequent treatment?	Small
7) Time on treatment	a. Should the company base case method or EAG-preferred method to modelling time on treatment be included in the model? b. Are high rates of discontinuation likely in NHS practice?	Small

Abbreviations: HSCT, hematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio

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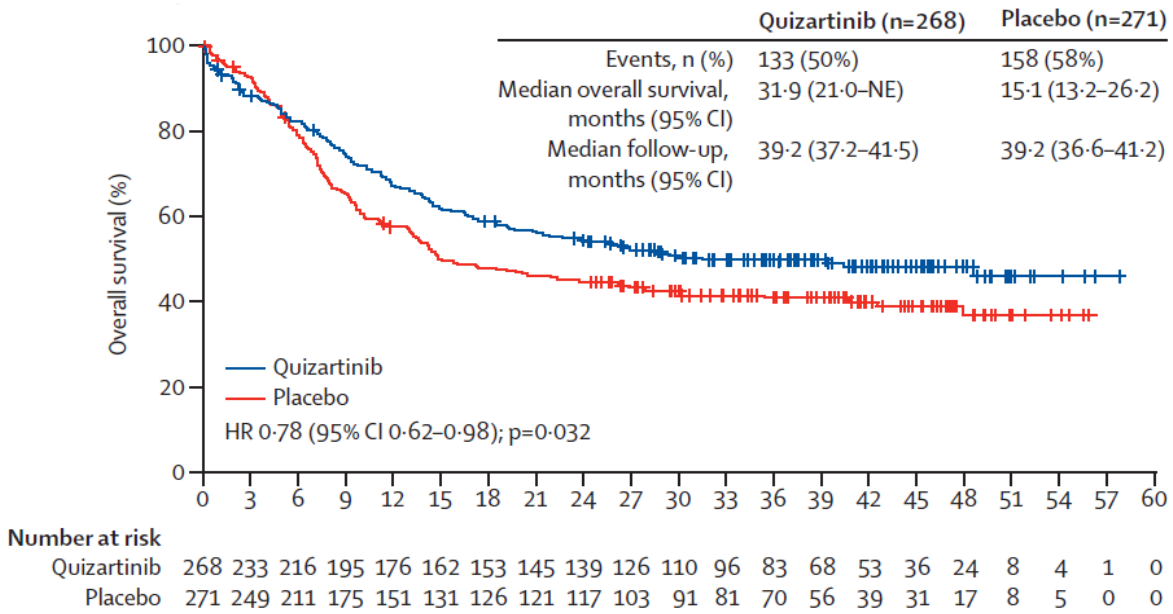
Clinical trial results: overall survival, primary outcome*

QuANTUM-First: phase 3, double-blind randomised trial, quizartinib vs placebo

Quizartinib vs placebo, overall survival KM plot



Restricted mean survival time (RMST), quizartinib	[redacted]
RMST, placebo	[redacted]
Difference	[redacted]

KM plot of OS for patients who entered maintenance phase with previous HSCT

[redacted]

EAG: crossing of KM curves in both graphs suggests proportional hazards assumption not met so HRs should be interpreted carefully

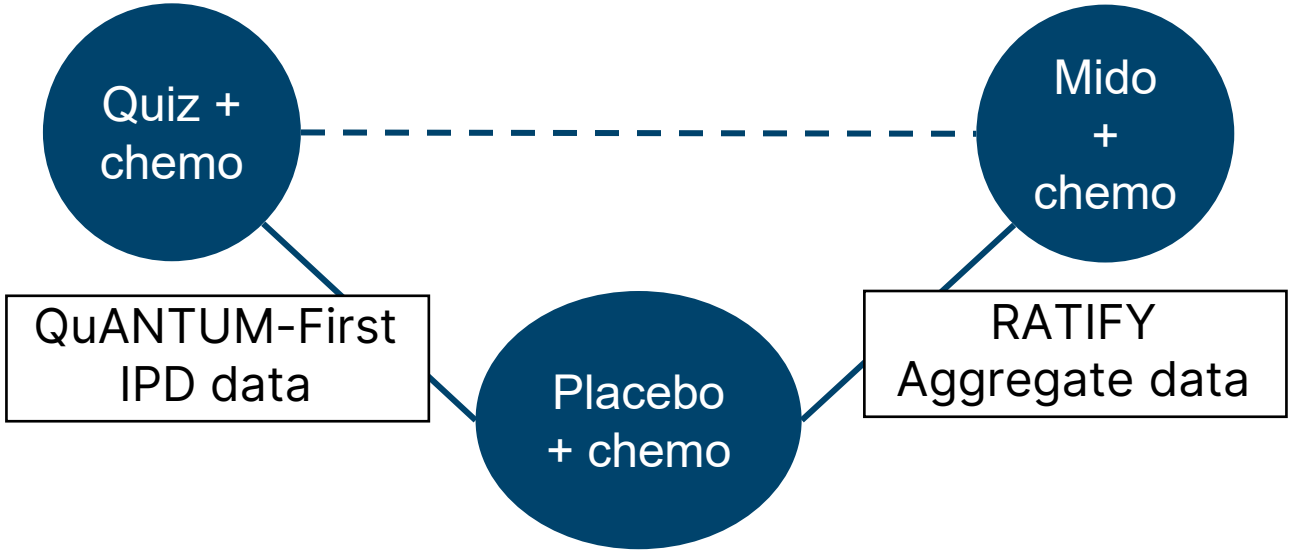
Abbreviations: KM, Kaplan-Meier; HR, hazard ratio; OS, overall survival; HSCT, haematopoietic stem cell transplant

[* see appendix – QuANTUM-First results]

Indirect treatment comparisons: methods*

Company presented ITCs for OS, CR and CIR after CR

*see link to Baseline characteristics, in the MAIC and ML-NMR



Outcomes
- Overall survival
- Complete remission
- Cumulative incidence of remission (proxy for relapse-free survival)

Treatment effect modifiers
- Platelet count
- Age
- Sex
- NPM1 mutation status

Matched-adjusted indirect comparisons (MAICs)

- Relative effect estimates calculated within FLT3-ITD mutation subgroup of RATIFY (n=555) so can only be used to model RATIFY-like population
- Used population <60 from QuANTUM-First to match RATIFY inclusion criteria
- Used as base case in economic model

Multilevel network meta-regressions (ML-NMRs)

- Allows generation of population averaged estimates that are applicable to any specified target population
- Fixed effects models used
- Used as scenario in economic model

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Abbreviations: IPD, individual patient-level data; ITC, indirect treatment comparison; OS, overall survival; CR, complete remission; CIR, cumulative incidence of relapse

Indirect treatment comparisons: results

Several results show no statistically significant benefit with quizartinib

Company's MAIC results (comparing QuANTUM-First <60 population and RATIFY)

Analysis	Comparison	OS	Complete remission (CR)	Cumulative incidence of relapse (CIR)
		HR (95% CI)	OR (95% CI)	HR (95% CI)
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)

Company's ML-NMR results (fixed effects)

QuANTUM-First-ITT like population	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's additional results (comparing QuANTUM-First all ages population and RATIFY)

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)

EAG: Results suggest adjustments applied within the company's ML-NMR favour quizartinib over midostaurin.

NB. HR<1 favours the first treatment over the second treatment in the comparison
OR>1 favours the first treatment over the second treatment in the comparison

Is there robust evidence of improved efficacy with quizartinib compared with midostaurin?

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Abbreviations: MAIC, matched-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; OS, overall survival; CR, complete remission; CIR, cumulative incidence of relapse; HR, hazard ratio; OR, odds ratio

Key issue: Comparability of trials in ITCs

Issue	RATIFY	QuANTUM-First	EAG comments
Timing of trial	2008-2016	2016-2021	Changes in clinical practice has improved treatment outcomes – RATIFY results not likely to be generalisable to current NHS practice and trials may not be comparable
Age included	18-59	18-75	Impacts applicability of company's MAIC results to people >60
CR data collection	CR only	CR and CRi - CRc rates calculated	CRi – can't assume equivalent for quizartinib and midostaurin CRc rates - used in NHS to measure response to induction

	EAG comments
Baseline characteristics	Some could not be compared across trials due to not being recorded or being recorded in a different format e.g. race, ECOG performance status, geographic region, WBC count, ELN risk group, cytogenetic risk status and abnormal karyotypes
HSCT	MRD analysis not used to guide treatment decision in either trial but is in NHS. Neither trial censored nor adjusted the analyses of CIR to account for patients receiving HSCT - any differences in HSCT rates across the trials would confound the ITCs of OS and CIR

Is it appropriate to compare QuANTUM-First and RATIFY in an indirect treatment comparison?

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Abbreviations: MAIC, matched-adjusted indirect comparison; CR, complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; CRc, composite complete remission; CIR, cumulative incidence of relapse; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; ELN, European LeukemiaNet; MRD, miniman or measurable residual disease; HSCT, hematopoietic stem cell transplantation; ITC, indirect treatment comparison; OS, overall survival

EAG additional analysis

Naïve indirect treatment comparison of QuANTUM-First and AMLSG 16-10

- To provide additional supportive evidence to address uncertainties in the ITCs, EAG conducted naïve comparison (in absence of patient-level data) of quizartinib and midostaurin using data from AMLSG 16-10
- AMLSG 16-10 was a non-randomised, open label, single arm trial of midostaurin (plus standard chemotherapy), that enrolled patients between 2012 and 2018, and compared with a historical cohort of patients treated with standard chemotherapy without midostaurin from five prior AMLSG trials
- Limitations:
  - Eligibility criteria for age were 18 to 75 years in QuANTUM-First and 18 to 70 years in the AMLSG 16-10 trial, however EAG notes median ages were similar (56 years vs 54.1 years respectively)
  - Assumes historical control group in AMLSG 16-10 (enrolled in trials between 1993 and 2009) and placebo group of QuANTUM-First (enrolled 2016-19) are common control group to anchor comparison
  - Restricted evidence base to match for all relevant treatment effect modifiers and prognostic factors
- Results suggest different directions and magnitudes of treatment effects compared with company's ITCs

Analysis	Comparison	OS	CR	CRc	CIR*
		HR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)
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)

*Data extracted for CIR from time of CRc for both studies.

Abbreviations: ITC, indirect treatment comparison; OS, overall survival; CR, complete remission; CRc, composite complete remission; CIR, cumulative incidence of relapse; HR, hazard ratio; CI, confidence intervals

Key issue: Reliability of indirect treatment comparisons (1)

EAG comments

Generalisability to NHS population

1. MAIC results are only applicable to a population like that in RATIFY, which is different to the NHS population
   - EAG considers that results of ML-NMR can be applicable to NHS population

CIR is analysed within subset of patients who reached CR, so randomisation is broken (probability of reaching CR is related to treatment received)

2. Patient characteristics of the subset of patients who achieved CR in quizartinib+chemo and placebo+chemo arms are likely imbalanced
3. Not appropriate to match characteristics of patients who reached CR in QuANTUM-First with all patients in FLT3-ITD+ subgroup of RATIFY
   - however, baseline characteristics of patients who reached CR within subgroup of RATIFY not available
4. Results of naïve comparisons for CIR do not align with results of MAIC or ML-NMR
   - implies that the matching and reweighting is favourable to quizartinib

Abbreviations: MAIC, matched-adjusted indirect comparison; CIR, cumulative incidence of relapse; CR, complete remission; ML-NMR, multilevel network meta-regression

Key issue: Reliability of indirect treatment comparisons (2)

EAG comments

Statistical issues with application of ITC results in the economic model

5. Both of the company's population-adjusted ITCs (MAICs and ML-NMRs) estimate a constant hazard ratio, which relies on the proportional hazards assumption
   - The presence of covariate effects violates this assumption
   - Would be better to use average survival curves for each treatment estimated by the ML-NMR in the model, rather than applying constant HRs
   - This approach could potentially be suitable for decision-making, but EAG does not have access to necessary data to implement this approach
6. Company's MAIC estimates marginal treatment effects (effect of moving everyone in target population from treatment with midostaurin to quizartinib) while ML-NMR estimates conditional treatment effects (average effect of moving each individual in target population from treatment with midostaurin to quizartinib) – different types of effects that need to be applied appropriately in the economic model
7. Company approach of applying conditional hazard ratio from ML-NMR to baseline KM curve unadjusted for treatment effect modifiers leads to aggregation bias (occurs when population-level effect estimate is applied to individual level data)

Are the results of the MAICs and the ML-NMR appropriate for decision-making?
Are the results of the ITCs applied correctly in the economic model?

Abbreviations: MAIC, matched-adjusted indirect comparison; CIR, cumulative incidence of relapse; CR, complete remission; ML-NMR, multilevel network meta-regression

Key issues: Efficacy and comparators in post-HSCT maintenance phase

Background

- QuANTUM-First not designed to estimate efficacy and safety of separate phases of quizartinib therapy
- Sorafenib is recommended through an NHS commissioning policy for post-HSCT maintenance

Company

- Sorafenib not included as comparator in maintenance phase in company's base case
- After clarification request, company provided unanchored MAIC to compare OS outcomes for quizartinib and sorafenib in post-HSCT maintenance setting using data from QuANTUM-First and SORMAIN (sorafenib vs placebo after HSCT)
- MAIC results*: HR [redacted]. Naïve comparison results: HR [redacted]

EAG comments

- Separate, relative effectiveness of quizartinib v placebo in consolidation and maintenance is uncertain and may be confounded by efficacy and safety of prior treatment phases
- Exploratory subgroup analysis (n=208 receiving maintenance therapy post-HSCT in QuANTUM-First) showed no benefit for quizartinib: OS HR 1.62 (95% CI: 0.62 to 4.22).
- MAIC results uncertain due to:
  - Lack of anchor or adjustment for all known treatment effect modifiers
  - Lack of evidence that the constant hazards assumption is met
  - Lack of evidence for outcomes other than OS, e.g. relapse
- Suggest an anchored MAIC, and an ITC of relapse-free survival may be feasible
- Evidence for efficacy and safety of sorafenib post-HSCT maintenance after induction and consolidation with midostaurin also lacking

*HR>1 favours sorafenib over quizartinib

Abbreviations: HSCT, hematopoietic stem cell transplantation; MAIC, matched-adjusted indirect comparison; HR, hazard ratio; OS, overall survival

Should sorafenib be included as a comparator in the post-HSCT maintenance phase?
Is the company's unanchored MAIC suitable for decision-making?

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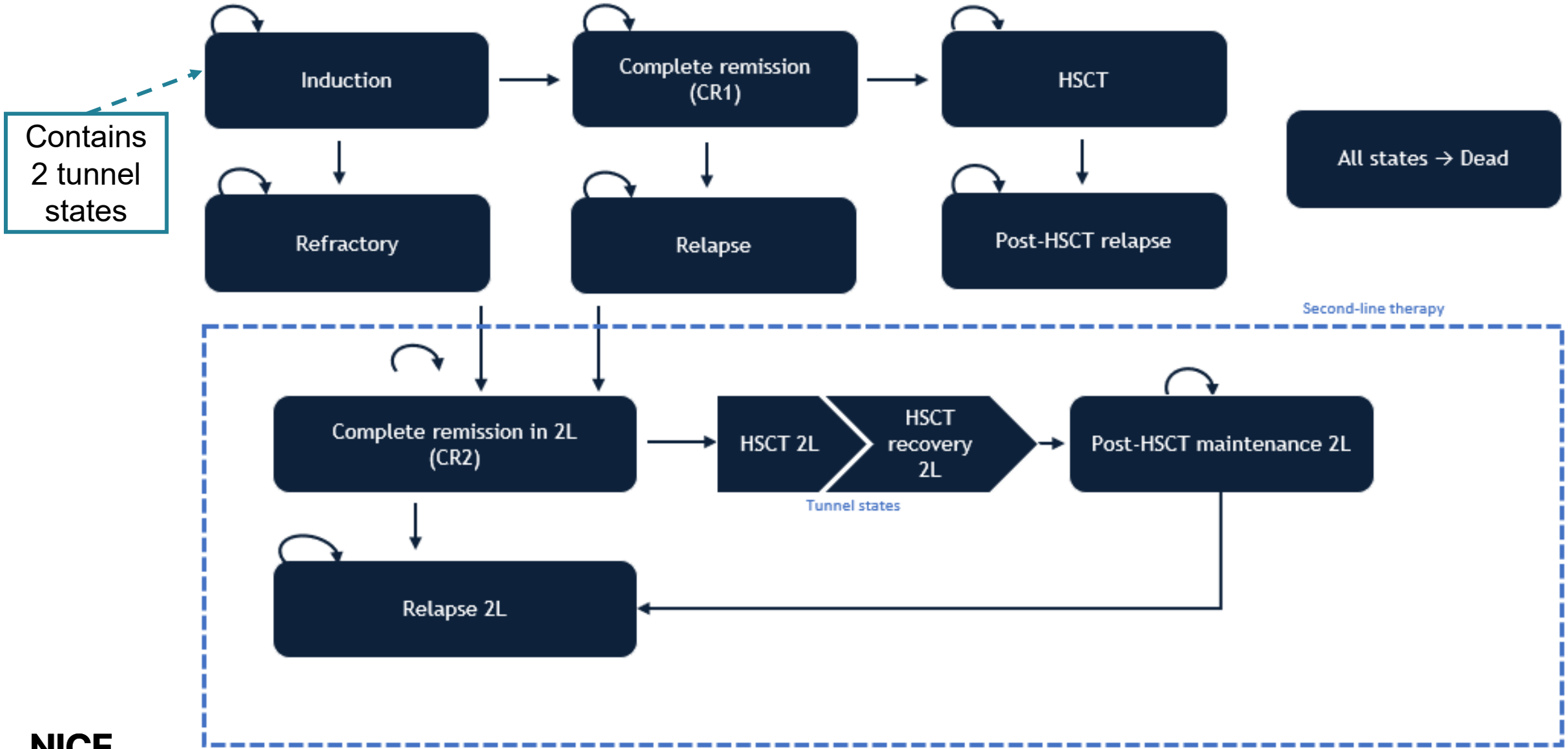
Model structure (1)

Company presents state transition model



Abbreviations: HSCT, hematopoietic stem cell transplant; 2L, second line; OS, overall survival; LY, life year; QALY, quality-adjusted life year; MAIC, matched-adjusted indirect comparison; ML-NMR, multilevel network meta-regression

Model structure (2)

EAG highlights differences between model results and ITC results

Company model

- Lifetime horizon
- Patients still in CR1 or HSCT (first line) at cycle 40 (~3y) are assumed to be cured – standard mortality ratio of 2 applied to general population mortality after this
- Baseline characteristics based on adjusted QuANTUM-First population (effectively RATIFY population)
- Standard chemotherapy (SC) arm, midostaurin arm and quizartinib arm modelled
    - SC arm reflects chemotherapy option in placebo arm of QuANTUM-First

EAG comments

- OS from trial not directly used in model – rates of remission, relapse, refractory disease and HSCT determine OS.
- Model predicts substantial LY and QALY gains for quizartinib vs midostaurin, primarily driven by treatment effect applied to relapse from CR – not in line with results from MAIC and ML-NMR of OS
- The company's base case 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.

Is the economic model suitable for decision making?
Are the results of the model valid, given the clinical evidence available?

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Abbreviations: HSCT, hematopoietic stem cell transplant; 2L, second line; OS, overall survival; LY, life year; QALY, quality-adjusted life year; MAIC, matched-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; CR, complete remission; ITC, indirect treatment comparison

Key issue: Treatment effectiveness in the model (1)

Company and EAG approaches to transitions from induction health state

Company

- Induction health state made of 2 sub-tunnel health states: induction 1 and 2
- Transition probabilities between induction 1 and induction 2 and for midostaurin, from induction state to CR1 state, are informed by MAIC analysis of complete remission
  - Odds ratio from MAIC primarily drives proportion of patients who move to a second induction, rather than overall proportion who reach complete remission

EAG comments

- Remission in the model is defined using CRc definition, and transition from induction to CR1 state informed by trial data on CRc for quizartinib and SC. But for midostaurin arm, transition based on MAIC for CR – not the same outcomes
  - Unavoidable with available data but increases uncertainty in model results.
- Company approach estimates proportion of patients moving to 2nd induction as residual of other transition probabilities.

EAG alternative approach

- EAG revises modelled population characteristics to align with QuANTUM-First population – notably mean age of modelled cohort increases from 47 to 54
- Use of QuANTUM-First population allows revision of calculations used in induction health state
- EAG approach estimates proportion of patients with refractory disease as residual.

Should the RATIFY-like population or QuANTUM-First population be the modelled population? Should the company's or EAG's approach to modelling induction state be used?

Abbreviations: MAIC, matched-adjusted indirect comparison; CR, complete remission; CRc, composite complete remission

Key issue: Treatment effectiveness in the model (2)*

Approaches to transitions from complete remission health state (first line)

Transition	Data and modelling	EAG comment	EAG base case
CR 1L to relapse	**Quiz:** time-to-relapse from CRc, QuANTUM-First adjusted to RATIFY-like population. Log-normal extrapolation. **SC and midostaurin**: HRs from MAIC of CIR applied to quiz curve.	MAIC of CIR is relapse events after CR (not CRc) and accounts for risk of death but does not censor for HSCT. Assumes that the HR generated from the MAIC of CIR can be transposed to the time to relapse from CRc outcome modelled. Also assumes proportional hazards, which are likely not met.*	Directly uses unadjusted QuANTUM-First data for quizartinib and SC with a generalised gamma extrapolation. For midostaurin, HR from the ML-NMR applied to SC arm.
CR 1L to death	**Quiz:** death from CRc, QuANTUM-First adjusted to RATIFY-like population. Log-normal extrapolation. **SC and midostaurin:** HRs from MAIC of OS applied to quiz curve.	MAIC of OS used is OS from time of randomisation, not conditional on CRc. Does not account for HSCT. Also relies on proportional hazards (likely not met). Observed trial data shows that the KM curves for OS from CRc (censored for relapse and HSCT) almost overlap slightly favouring SC.*	Uses unadjusted QuANTUM-First trial data with a Gompertz extrapolation. Assumes mortality rates after CRc are the same in quizartinib and midostaurin arm.

Abbreviations: CR, complete remission; 1L, first line; CRc, composite complete remission; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; CIR, cumulative incidence of relapse; HSCT, hematopoietic stem cell transplant; OS, overall survival; KM, Kaplan-Meier; ML-NMR, multilevel network meta-regression; SC, standard chemotherapy

Is the company approach or EAG approach more reliable for the transitions from the complete remission health state?

*Link to appendix

Key issue: Treatment effectiveness in the model (3)

Company and EAG approaches to transitions from HSCT health state

Transition	Company data and modelling	EAG comment	EAG base case
HSCT 1L to relapse	Time invariant transition probabilities from QuANTUM-First. Midostaurin assumed equivalent to SC.	Inconsistent to use time invariant probabilities for transition to relapse but time-varying approach for overall survival. DSU advice is that that usually, same type of parametric model should be used in both arms.	Uses time-varying approach for both transitions: HSCT 1L to relapse transition uses KM data from the adjusted QuANTUM-First population and a generalised gamma extrapolation for both arms.
HSCT 1L to death	Post-protocol-specified HSCT survival data from QuANTUM-First adjusted to RATIFY-like population, censored for relapse. **Quizartinib:** Gompertz extrapolation **SC:** Generalised gamma extrapolation **Midostaurin**: Assumed equivalent to SC.		

Should the transition from HSCT 1L to relapse be based on time invariant probabilities from QuANTUM-First, or KM data from QuANTUM-First with a generalised gamma extrapolation?

Abbreviations: HSCT, hematopoietic stem cell transplant; SC, standard chemotherapy; DSU, decision support unit; 1L, first line; KM, Kaplan-Meier

Key Issue: Second-line treatment modelling

Background

- In TA523, committee highlighted several limitations of using a partitioned survival model e.g. couldn't account for benefit of second line treatment
- TA642 recommends gilteritinib for relapsed or refractory FLT3+ AML – cure model accepted

Company

- Uses state transition model which allows effectiveness of gilteritinib to be modelled even though not included in QuANTUM-First or RATIFY – transition probabilities between health states drawn from ADMIRAL trial. Cure not modelled in second line.
- Model assumes all patients with relapsed or refractory disease have subsequent treatment with FLAG-Ida or gilteritinib – distribution based on whether 1st or 2nd generation FLT3 inhibitor received in first line

EAG comments

- Prefers to use nested partitioned survival model for second line and for patients who relapse after HSCT as state transition model difficult to populate accurately without individual patient-level data
- Includes possibility of cure with second-line treatment
- Company model does not allow patients to reach remission after HSCT relapse
- Clinical advice suggests in practice most people would have gilteritinib in second line regardless of previous treatment, so proportion receiving gilteritinib in model is underestimated. EAG base case: 90%.

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Should second-line treatment be modelled using a state transition or partitioned survival model?
Should cure be possible after second-line treatment?
Should remission after HSCT relapse be possible in the model?
What proportion of people are likely to have gilteritinib as subsequent treatment?

Abbreviations: FLT3, FMS-like tyrosine kinase 3; AML, acute myeloid leukaemia; HSCT, hematopoietic stem cell transplant; FLAG-Ida, fludarabine, cytarabine, granulocyte- colony stimulating factor and idarubicin

Key Issue: Time on treatment

Company's updated scenario analysis resolves issue but not included in base case

Company

- In base case, modelled time on treatment calculated using a restricted mean, due to incomplete trial follow-up in QuANTUM-First
- In response to EAG comments, conducted scenario analysis to implement EAG-preferred method but did not include this in its base case

EAG comments

- Considers that time on treatment is underestimated in company base case and so drug costs are also underestimated
  - Single mean relative dose intensity (RDI) applied across all treatment phases although in QuANTUM-First, RDI differed across treatment phases
  - Restricted mean accounts for censoring due to incomplete follow-up but underestimates the mean survival time if all events had occurred. Unrestricted mean could be calculated by extrapolation of observed data
  - Approach also double-counts impact of relapse, HSCT and OS events
- In QuANTUM-First, there was low adherence and high levels of discontinuation – most patients did not complete full maintenance course of 36 cycles

Should the company base case method or EAG-preferred method to modelling time on treatment be included in the model?
Are high rates of discontinuation likely in NHS practice?

Abbreviations: HSCT, hematopoietic stem cell transplant; OS, overall survival

Summary of company and EAG base case assumptions (1)

Assumption	Company base case	EAG base case	Slide
Model structure for second line	State transition model	EAG-preferred PSM structure, including: • Cure assumption after 3 years • Remission after HSCT relapse	26
Population	RATIFY-like population, including transition probabilities informed by MAICs	QuANTUM-First ITT population, including: • Mean age amended • Reconfiguration of induction state • Relapse and OS data for quiz based on QuANTUM-First and ML-NMRs, with EAG-preferred extrapolations for CRc to relapse (generalised gamma) and CRc to death (Gompertz)	23 23 24
Transitions from HSCT	Time-invariant transition probabilities for relapse events	KM data for relapse post-HSCT 1L	25
Subsequent treatment	Based on which treatment received first line	90% receive gilteritinib	26
Time on treatment	Company approach	EAG approach plus RDI applied by phase	27
Utility values	Based on published values	Based on QuANTUM-First	45

Abbreviations: PSM, partitioned survival model; MAIC, matched-adjusted indirect comparison; HSCT, hematopoietic stem cell transplant; ITT intention-to-treat; OS, overall survival; CRc, composite complete remission; OS, overall survival; KM, Kaplan-Meier; RDI, relative dose intensity

Cost-effectiveness results

Deterministic results

- All cost-effectiveness results are presented in part 2 because they contain confidential prices for the comparators/subsequent treatments.

Company base case	Fully inc. ICER (£/QALY)
SC regimen	-
Midostaurin regimen	<£30,000
Quizartinib regimen	<£30,000

EAG base case	Fully inc. ICER (£/QALY)
SC regimen	-
Midostaurin regimen	>£30,000
Quizartinib regimen	>£30,000

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SC, standard chemotherapy

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

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Key issues (1)

Key:
Large Small Unknown

Key issues	ICER impact	Slide
1) Comparators: Is standard chemotherapy alone a relevant comparator?	Large	7
2) Indirect treatment comparisons: Is there robust evidence of improved efficacy with quizartinib compared with midostaurin, in terms of overall survival, complete remission or cumulative incidence of relapse? a. Is it appropriate to compare QuANTUM-First and RATIFY in an indirect treatment comparison? b. Are the results of the MAICs and the ML-NMR appropriate for decision-making? c. Are the results of the ITCs applied correctly in the economic model?	Unknown	15-18
2) Economic model results: Is the economic model suitable for decision making? Are the results of the model valid, given the clinical evidence available? • Should the RATIFY-like population or QuANTUM-First population be the modelled population? • Should the company's or EAG's approach to modelling induction state be used? • Is the company approach or EAG approach more reliable for the transitions from the complete remission health state?	Large	22-23

Abbreviations: MAIC, matched-adjusted indirect treatment comparison; ML-NMR, multilevel network meta-regression; HSCT, hematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; CR, complete remission; 1L, first-line; KM, Kaplan-Meier

Key issues (2)

Key:
Large Small Unknown

Key issues	ICER impact	Slide
4) Maintenance phase: a. Should sorafenib be included as a comparator in the post-HSCT maintenance phase? b. Is the company's unanchored MAIC suitable for decision-making?	Unknown	19
5) Post-HSCT treatment effectiveness: Should the transition from HSCT 1L to relapse be based on time invariant probabilities from QuANTUM-First, or KM data from QuANTUM-First?	Small	24
6) Second-line treatment modelling: a. Should second-line treatment be modelled using a state transition or partitioned survival model? b. Should cure be possible after second-line treatment? c. Should remission after HSCT relapse be possible in the model? d. What proportion of people are likely to have gilteritinib as subsequent treatment?	Small	25
7) Time on treatment: a. Should the company base case method or EAG-preferred method to modelling time on treatment be included in the model? b. Are high rates of discontinuation likely in NHS practice?	Small	27

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Abbreviations: HSCT, hematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio

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

Supplementary appendix

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Decision problem (1)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People with newly diagnosed AML that is *FLT3-ITD+*	Aligned with NICE scope	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)	The intervention described in the CS is in line with the NICE scope and its EMA / MHRA licenced indication.

Abbreviations: AML, acute myeloid leukaemia; CS, company submission; FLT3-ITD, Feline McDonough sarcoma-like tyrosine kinase 3 internal tandem duplication

Decision problem (2)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
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 chemotherapy drugs.	**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.	Agrees with comparator treatments during induction and consolidation phases. Disagrees with exclusion of sorafenib as comparator in post-HSCT maintenance. Sorafenib is recommended by NHS England since November 2023 as a routine commissioning treatment option for adults with *FLT3-ITD*+ AML undergoing allo-HSCT. Clinical advice to EAG confirmed that sorafenib is now widely used in this setting.

Abbreviations: AML, acute myeloid leukaemia; FLT3-ITD, Feline McDonough sarcoma-like tyrosine kinase 3 internal tandem duplication; HSCT, hematopoietic stem cell transplant; CR, complete remission

Decision problem (3)

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Outcomes	• Overall survival • Event-free survival • Relapse-free survival • Adverse effects of treatment	• 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	N/A

QuANTUM-First results: secondary and additional outcomes

	Quizartinib (N=268)	Placebo (N=271)
Event-free survival events, (IRC assessment, FDA definition of ITF) n (%)	198 (73.9)	213 (78.6)
EFS 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)
Complete remission rate (%) (95% CI[d])	54.9 (48.7, 60.9)	55.4 (49.2, 61.4)
Median duration of CR (95% CI), months	38.6 (21.9, NE)	12.4 (8.8, 22.7)
Duration of CR 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)
Cumulative incidence of relapse events, n (% of patients with CR)	44 (30)	63 (42)
CIR HR (95% CI)		[redacted]
Protocol-specified HSCT: Rate (%) (95% CI)[g]	38.1 (32.2, 44.2)	33.6 (28.0, 39.5)
Protocol-specified HSCT and non-protocol-specified HSCT: Rate (%) (95% CI)	53.7 (47.6, 59.8)	47.2 (41.2, 53.4)

Link to Clinical trial results: overall survival, primary outcome

Abbreviations: EFS, event-free survival; HR, hazard ratio; CI, confidence intervals; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; HSCT, haematopoietic stem cell transplant

QuANTUM-First results: safety (1)

Study drug-related treatment-emergent adverse events

Link to Clinical trial results: overall survival, primary outcome

Category	Quizartinib (N = 265)			Placebo (N = 268)		
	All grades n (%)	Grade ≥3	Grade 3/4 n (%)	All grades n (%)	Grade ≥3	Grade 3/4 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]
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]

Rates of neutropenia and QT prolongation considered to be treatment-related were more frequent in the quizartinib arm. Most QT prolongation were non-serious and resolved, but cardiac deaths were reported in the quizartinib arm. EMA stated that, based on trial, “impact of cardiac risks may be underestimated”. More early deaths observed in quizartinib arm, mostly due to infections

Baseline characteristics in RATIFY and QuANTUM-First

A number of characteristics not reported across both trials

Characteristics	QuANTUM-First		RATIFY	
	FLT3-ITD (ITT)		FLT3-ITD	
	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)
FLT3-ITD with low allelic ratio (<0.5), n(%)	[redacted]	[redacted]	80 (34.8)	81 (36.6)
FLT3-ITD with high allelic ratio (>0.5), n(%)	[redacted]	[redacted]	149 (65.2)	141 (63.4)
NPM1 mutation n, (%)	142 (53.0)	140 (51.7)	95 (50.0)	108 (64.3)
Median platelet counts $10^3/\mu L$ (range)	[redacted]	[redacted]	51 (2, 461)	50 (8, 342)
Median bone marrow blast count (range), n	[redacted]	[redacted]	77 (3, 100)	80 (6, 100)

Not reported in QuANTUM-First: ELN risk group, abnormal karyotypes. Not reported in RATIFY: Race, ECOG performance status, absolute neutrophil count, region, cytogenetic risk status. White blood cell count at diagnosis reported differently between 2 trials.

NICE

Abbreviations: FLT3-ITD, Feline McDonough sarcoma-like tyrosine kinase 3 internal tandem duplication; ITT, intention-to-treat; ELN, European LeukemiaNet; ECOG, Eastern Cooperative Oncology Group

Link to Indirect treatment comparisons: methods

Patient characteristics included in the MAIC

MAIC comparing quizartinib (QuANTUM –First population up to age 60) and midostaurin (RATIFY FLT3-ITD+ population)

Matching variable	QuANTUM-First unadjusted (N=[redacted])	QuANTUM-First Adjusted (ESS=[redacted])	RATIFY FLT3-ITD population (N=[redacted])
TEMs (Base case)			
Platelet count x 10^9/L, mean	[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	[redacted]	[redacted]	47
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)

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Abbreviations: MAIC, matched-adjusted indirect comparison; TEM, treatment effect modifier; NPM1, nucleophosmin 1; ESS, estimated sample size; FLT3-ITD, FMS-like tyrosine kinase 3 internal tandem duplication

Link to Indirect treatment comparisons: methods

ML-NMR baseline characteristics: complete remission

CR and baseline characteristics employed in ML-NMR

Baseline characteristic	QuANTUM-First ITD	QuANTUM-First ITD <60 years	RATIFY ITD+ population
Age, mean	54.0	[redacted]	47.1
Age, sd	12.9	[redacted]	NR
Sex, male, %	45	[redacted]	45
Platelet count, x 10^9/l, mean	30.0	[redacted]	44.6
Platelet count, x 10^9/l, sd	28.7	[redacted]	NR
NPM1 mutation status, positive, %	52	[redacted]	57
OR (95% CrI)	0.99 (0.70-1.39)	[redacted]	1.30 (0.87-1.93)

Link to Indirect treatment comparisons: methods

Abbreviations: ITD, internal tandem duplication; CR, complete remission; ML-NMR, multilevel network meta-regression; OR, odds ratio; CrI, credible intervals; NPM1, nucleophosmin 1; NR, not reported

Treatment effectiveness in the model: CR to relapse/death

Proportion of patients reaching cure point of 3 years

EAG comments

The structural assumption of 'functional' cure applied at 3 years in the model means that the observed data does not need to be extrapolated, because the duration of trial follow-up is beyond 3 years. 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.

	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]

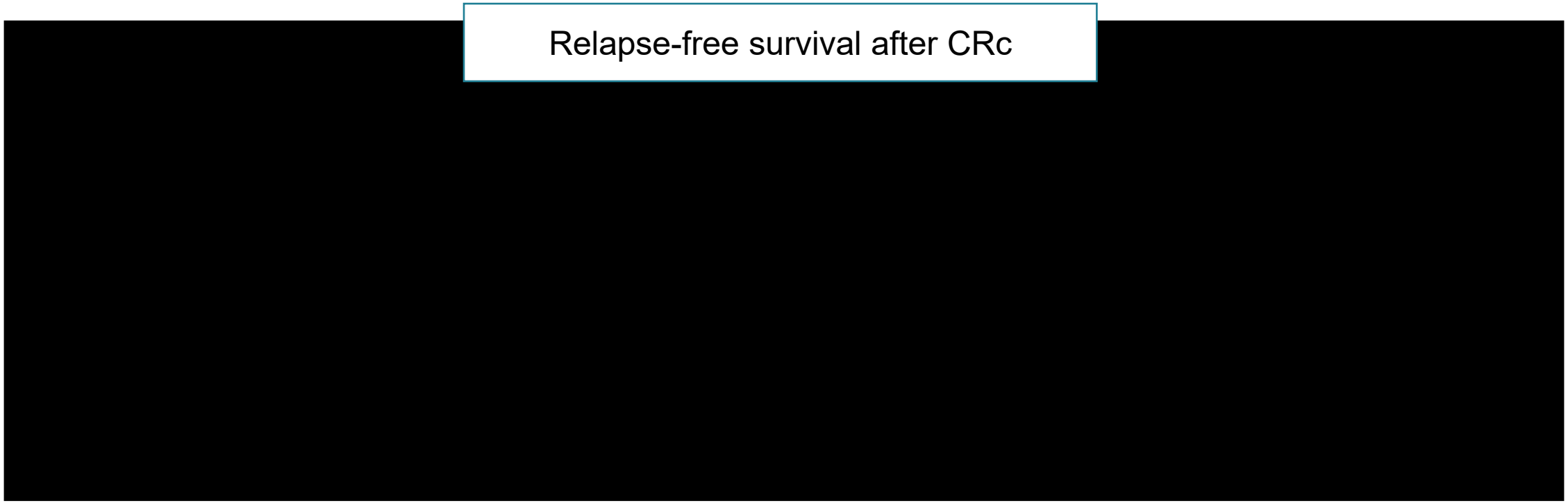
Link to Key issue: Treatment effectiveness in the model (2)

Abbreviations: SC, standard chemotherapy; CRc, complete composite remission; KM, Kaplan-Meier

Treatment effectiveness in the model: CR

Bias when applying HR to survival curve when proportional hazards not met

- Pink curve is SC relapse from CRc survival curve generated using HR (company's method)
- Black curve is lognormal parametric curve applied to KM survival data from QuANTUM-First, adjusted to RATIFY-like population
- Company's approach significantly underestimates survival outcomes for SC

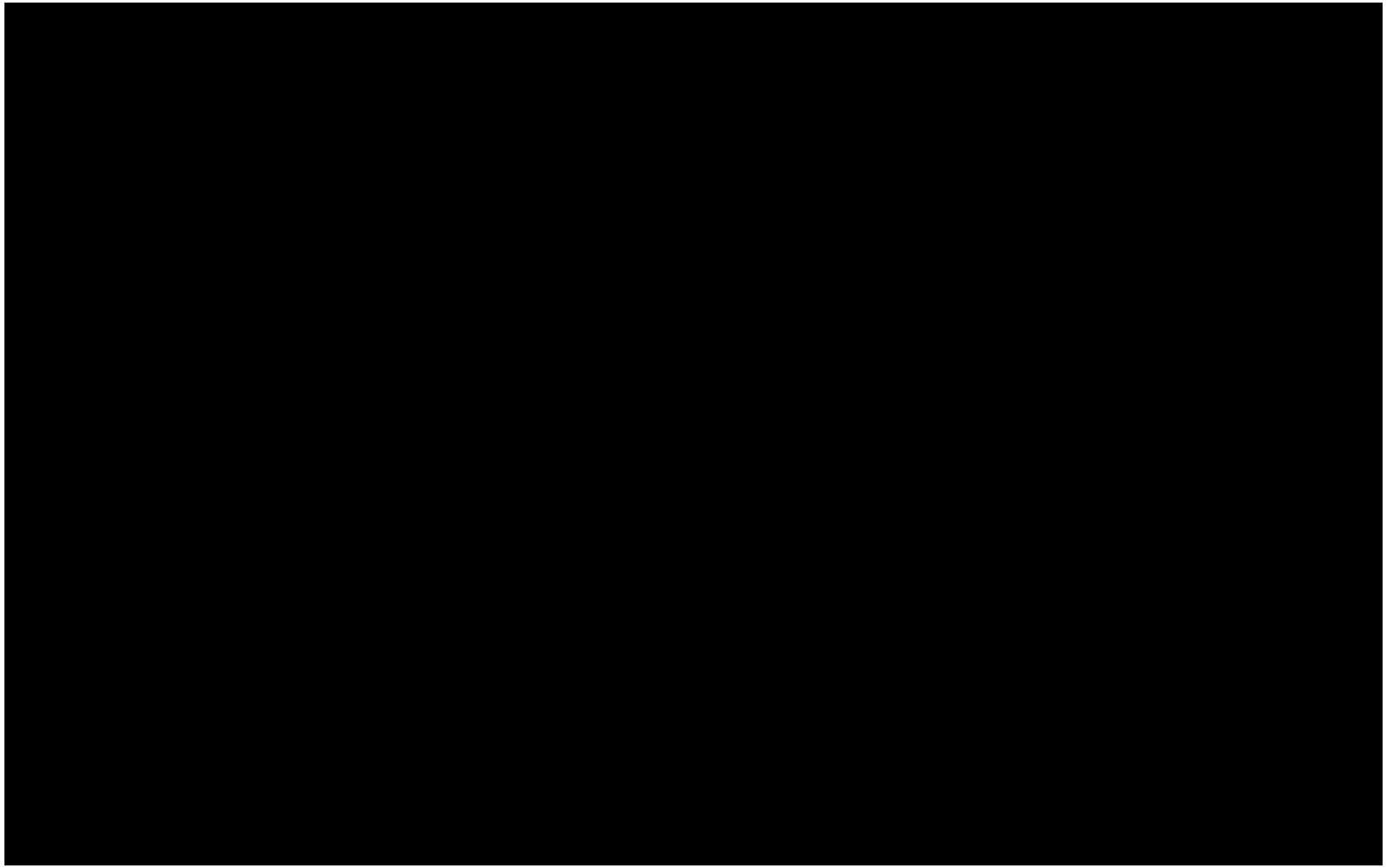


Abbreviations: CR, complete remission; CRc, composite complete remission; HR, hazard ratio; SC, standard chemotherapy; KM, Kalpan-Meier

Link to Key issue: Treatment effectiveness in the model (2)

Treatment effectiveness in the model

Kaplan-Meier curve for overall survival after complete composite remission



Key Issue: Utility values

Company sourced utility values from literature

Company

- Used utility values from several sources in the literature, based on values used in TA523 and mapped to health states based on clinical expert opinion

EAG comments

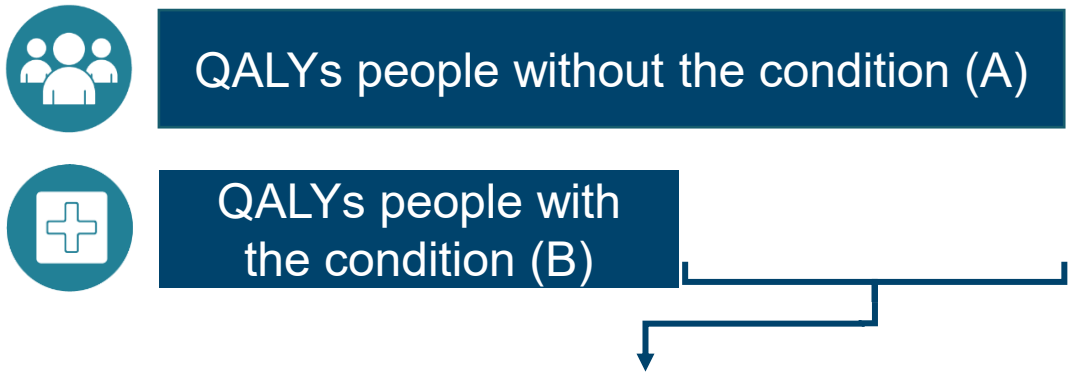
- Utility values sourced from literature in TA523 because patient-reported outcomes not available in trial
- TA642 used trial-based utilities
- EQ-5D data was collected in QuANTUM-First so EAG base case uses observed trial utility values.

Should the utility values be based on published values or QuANTUM-First?

Abbreviations: EQ-5D, EuroQol-5 dimension

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity (2/2)

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	Absolute QALY shortfall (has to be >12)	Proportional QALY shortfall (has to be >0.85)
Company base case (EAG corrected)	Midostaurin: 16.69 SC: 16.69	Midostaurin: [redacted] SC: [redacted]	Midostaurin: 10.94 SC: 11.95	Midostaurin: 0.66 SC: 0.72
Company base case (DSU calculator)	Midostaurin: 16.80 SC: 16.80	Midostaurin: [redacted] SC: [redacted]	Midostaurin: 11.05 SC: 12.07	Midostaurin: 0.66 SC: 0.72
EAG base case	Midostaurin: 14.57 SC: 14.57	Midostaurin: [redacted] SC: [redacted]	Midostaurin: 9.66 SC: 9.98	Midostaurin: 0.66 SC: 0.68
EAG base case (DSU calculator)	Midostaurin: 14.70 SC: 14.70	Midostaurin: [redacted] SC: [redacted]	Midostaurin: 9.79 SC: 10.11	Midostaurin: 0.67 SC: 0.69

- DSU calculator published after company submission – EAG has provided values using this calculator.
- Absolute QALY shortfall above 12 using DSU calculator in company base case, compared with SC. EAG considers midostaurin is the main comparator so severity modifier of 1 is applicable.
- No severity modifier included in company or EAG base case or any scenarios.

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Abbreviations: QALY, quality-adjusted life year; SC, standard chemotherapy; DSU, Decision Support Unit

Effect of EAG deterministic scenario analysis on company ICERs (1)

	Regimen	Fully inc. ICER (£/QALY)
Company base case	**SC**	
	Midostaurin	**<£30,000**
	Quizartinib	**<£30,000**
1a) PSM structure	SC	
	Midostaurin	↑ Increase
	Quizartinib	↓ Decrease
1b) PSM structure + calculation errors	SC	
	Midostaurin	↑ Increase
	Quizartinib	↓ Decrease
1c) PSM structure + Cure (PSM model)	SC	
	Midostaurin	↑ Increase
	Quizartinib	↓ Decrease
1d) EAG preferred configuration of PSM	SC	
	Midostaurin	↑ Increase
	Quizartinib	↑ Increase

Abbreviations: PSM, partitioned survival model; SC, standard chemotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Effect of EAG deterministic scenario analysis on company ICERs (2)

	Regimen	Fully inc. ICER (£/QALY)
2b) QuANTUM-First population + Induction reconfigured	SC	
	Midostaurin	↑ Increase
	Quizartinib	↑ Increase
2f) QuANTUM-First population + ML-NMR + direct RFS and OS + preferred extrapolations	SC	
	Midostaurin	↑ Increase
	Quizartinib	↑ Increase
3) KM data for post-HSCT relapse	SC	
	Midostaurin	↑ Increase
	Quizartinib	↓ Decrease
4) QuANTUM-First HRQoL	SC	
	Midostaurin	↑ Increase
	Quizartinib	↓ Decrease
5b) Assuming 90% of patients receive gilteritinib	SC	
	Midostaurin	↑ Increase
	Quizartinib	↓ Decrease

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SC, standard chemotherapy; ML-NMR, multilevel network meta-regression; RFS, relapse-free survival; OS, overall survival; KM, Kaplan-Meier; HSCT, hematopoietic stem cell transplant; HRQoL, health-related quality of life

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.