SMC2699

quizartinib film-coated tablets (Vanflyta®)

Daiichi Sankyo UK Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

quizartinib (Vanflyta®) is accepted for use within NHSScotland.

Indication under review: 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 FLT3-ITD positive.

In a randomised, double-blind, phase III study, the addition of quizartinib compared with placebo to standard chemotherapy significantly improved overall survival in newly diagnosed patients with AML with FLT3-ITD mutation.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Quizartinib is selective type II tyrosine kinase FMS-like tyrosine kinase 3 (FLT3) receptor inhibitor, which together with its major metabolite, prevents autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-internal tandem duplication (ITD)-dependent cell proliferation.[1, 2]

Quizartinib should be administered in combination with standard chemotherapy at a dose of 35.4 mg orally once daily for 2 weeks in each cycle of induction. For patients who achieve complete remission or complete remission with incomplete haematologic recovery, quizartinib 35.4 mg daily should be administered once daily for 2 weeks in each cycle of consolidation chemotherapy, followed by quizartinib single-agent maintenance therapy initiated at 26.5 mg once daily for 2 weeks, increased to 53 mg once daily if the QT interval corrected by Fridericia's formula (QTcF) is ≤450 milliseconds. Single-agent maintenance therapy may be continued for up to 36 cycles of 28 days.[2] Refer to Summary of Product Characteristics (SPC) for further information.

1.2. Disease background

Acute myeloid leukaemia (AML) is a heterogeneous, life-threatening, haematological malignancy that is more common in older adults. It is characterised by genetic abnormalities in haematopoietic precursor cells (granulocytes and monocytes) which result in accumulation of abnormal myeloid blasts in the bone marrow that are unable to differentiate into mature neutrophils, red blood cells, or platelets. These immature cells block the development of healthy blood cells and may spill out into the blood where they are unable to work normally.[3]

Overexpression of the FLT3 receptor occurs in nearly all cases of AML and mutations in FLT3 represent one of the most common genetic alterations, occurring in approximately 30% of adult patients with newly diagnosed AML. There are two subtypes of FLT3 mutation: ITD and tyrosine kinase domain (TKD). The FLT3-ITD mutation is more common and is found in 20% to 25% of all AML cases compared with the TDK mutation which is found in 7% to 10%. Patients with AML and a FLT3-ITD mutation are at higher risk of relapse than patients without this mutation and they have a poorer prognosis. The median time to relapse for patients with FLT3-ITD mutated AML in first remission is estimated to be approximately 9 months.[1]

1.3. Treatment pathway and relevant comparators

Chemotherapy is the mainstay of treatment for patients with newly diagnosed AML. This can generally be divided, depending on eligibility (fitness and ability to cope with treatment) and patient preference, into intensive, which aims at cure, and non-intensive, which aims to control disease. Standard intensive treatment includes induction chemotherapy with cytarabine plus an anthracycline. For patients who achieve a complete remission, consolidation therapy and / or an allogeneic haematopoietic stem cell transplantation (HSCT) is recommended to eradicate residual disease and prevent relapse. However, despite this approach, relapse remains high and there is a high risk of mortality due to allo-HSCT.[1, 4]

More recently, multikinase inhibitors targeting the FLT3 mutations have improved outcomes for these patients. Midostaurin is licensed for use in combination with standard daunorubicin and

cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single-agent maintenance therapy, for adult patients with newly diagnosed AML who are FLT3 mutation-positive. This is accepted for use by SMC (SMC1330/18).[1, 5]

There is no standard therapy for patients with relapsed or refractory disease and depending on suitability, patients may receive intensive or low-intensity salvage chemotherapy. Gilteritinib is a FLT3 inhibitor licensed for use in patients who have relapsed or refractory AML with a FLT3 mutation and is accepted for use by SMC (SMC2252).

1.4. Category for decision-making process

Eligibility for a PACE meeting

Quizartinib meets SMC orphan criteria

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of quizartinib for the treatment of newly diagnosed AML comes from the QuANTUM-First study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[1, 6]

Criteria	QuANTUM-First
Study design	International, randomised, double-blind, phase III study.
Eligible patients	• Patients aged 18 to 75 years and suitable for standard induction chemotherapy • Morphologically documented primary newly diagnosed AML or AML secondary to myelodysplastic syndrome or myeloproliferative neoplasm • FLT3-ITD mutation identified by central laboratory assessment in bone marrow or peripheral blood • ECOG performance status of 0 to 2.
Treatments	<table><tr><th>Phase</th><th>Standard chemotherapy</th><th>Randomised treatment</th></tr><tr><td>Induction (up to two 28-day cycles)</td><td>cytarabine 100 mg/m^2/day or 200 mg/m^2/day continuous IV infusion on days 1 to 7. Anthracycline (daunorubicin [60 mg/m^2/day IV on days 1, 2, and 3] or idarubicin [12 mg/m^2/day IV on days 1, 2, and 3]).</td><td rowspan="2">quizartinib 35.4 mg or placebo orally once daily for 14 days of each induction and consolidation cycle (induction cycle: days 8 to 21; consolidation cycle: days 6 to 19), followed by quizartinib[B] 26.5 mg or placebo orally daily during maintenance</td></tr><tr><td>Consolidation (up to four cycles of up to 60 days)[A]</td><td>cytarabine 3,000 mg/m^2 if <60 years old or 1,500 mg/m^2 if ≥60 years old, IV every 12 hours on days 1, 3, and 5</td></tr></table>

	Maintenance (up to thirty-six 28-day cycles	-	
	[A] during consolidation phase there were three options: consolidation chemotherapy followed by quizartinib or placebo (as described); allogeneic HSCT; or, consolidation chemotherapy followed by quizartinib or placebo (as described) followed by allogeneic HSCT [B] quizartinib could be increased to 53 mg daily if the mean QTcF of the triplicate echocardiogram was ≤450 milliseconds on day 15 of cycle 1		
Randomisation	Patients were randomised equally to receive quizartinib or placebo with stratification for: geographical region (Europe, North America or Asia, Australia and South America), age (<60 years and ≥60 years) and WBC count at diagnosis (<40 x 10^9/L and ≥40 x 10^9/L).		
Primary outcome	Overall survival defined from time of randomisation to death from any cause.		
Secondary outcomes	• EFS, defined as time from randomisation to lack of complete remission within 42 days from the start of the last cycle of induction chemotherapy, relapse or death from any cause assessed by IRC. • CR rate assessed by IRC, defined as achieving >1,000 neutrophils, >100,000 platelets, <5% blasts, no extramedullary disease, no Auer rods and an absence of leukaemic blasts in the peripheral blood by morphological examination • Rate of patients achieving CR with FLT3-ITD MRD negativity • CRc rate defined as composite of CR (above) or CRi • Rate of patients achieving CRc with FLT3-ITD MRD negativity		
Statistical analysis	A hierarchical statistical testing strategy was applied in the study for the primary and key secondary outcomes (in the order above) with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore, the results reported for these outcomes are descriptive only. Efficacy was assessed in the ITT population which included all randomised patients.		

AML = acute myeloid leukaemia; CR = complete remission; CRc = composite complete remission; CRi = complete remission with incomplete neutrophil or platelet recovery; ECOG = Eastern Co-operative Oncology Group; EFS = event-free survival; HSCT = haematopoietic stem cell transplantation; IRC = independent review committee ITT = intention to treat; IV = intravenous; MRD = measurable residual disease; WBC = white blood cell

After a median follow-up of 39.2 months (data cut-off 13 August 2021), median overall survival (OS) was significantly longer in patients in the quizartinib group compared with the placebo group. There was no statistically significant difference between quizartinib and placebo for the first secondary outcome of EFS. Therefore, further formal statistical testing was not performed and the results reported for subsequent outcomes are descriptive only and not inferential (no p-values reported). Details are presented in Table 2.2.

Table 2.2: Results for primary and key secondary outcomes in the ITT population of QuANTUM-First[1, 6]

	Quizartinib (n=268)	**Placebo (n=271)**
Primary outcome: OS		
Median duration of follow-up, months	39.2	39.2
Number of deaths	133	158
Median OS, months	31.9	15.1
Hazard ratio (95% CI), p-value	0.78 (0.62 to 0.98), p=0.032	
Kaplan-Meier estimate of OS rate		
12 months	67%	58%
24 months	55%	45%
36 months	50%	41%
48 months	48%	37%

Secondary outcomes		
Number of EFS events, n	198	213
Median EFS, months	0.03	0.71
Hazard ratio (95% CI)	0.92 (0.75 to 1.11)	
CR	55%	55%
CRc	72%	65%
CR with FLT3-ITD MRD negativity	20%	19%

CI = confidence interval; CR = complete remission; CRc = composite complete remission; EFS = event-free survival; MRD = measurable residual disease; OS= overall survival.

A prespecified sensitivity analysis of OS was performed, censoring patients who had an allogeneic HSCT (144 in the quizartinib group and 128 in the placebo group); median OS was 20.8 months versus 12.9 months respectively (HR 0.75 [95% CI 0.56 to 1.01]).[6]

Results of predefined subgroup analyses of OS based on age, sex, race, and geographical region, as well as baseline disease characteristics (Eastern Co-operative Oncology Group (ECOG), white blood cell (WBC) count at diagnosis, choice of anthracycline during induction, AML cytogenetic risk score, FLT3-ITD variant allelic frequency at randomisation, and nucleophosmin 1 [NPM1] mutational status) were generally consistent with the ITT population, favouring quizartinib over placebo. There were three exceptions: patients from North America (n=34); patients with a favourable AML cytogenetic risk score (n=33) and patients with no NPM1 mutation (n=236). In a further post hoc analysis of OS by age, the hazard ratio was 0.68 (95% CI 0.49 to 0.95) in patients aged <60 years (n=323) and 0.91 (95% CI 0.66 to 1.26) in patients aged ≥60 years (n=216).[1, 6]

Additional relevant exploratory outcomes included relapse-free survival (RFS, defined as time from randomisation until date of documented relapse or death from any cause) in patients with CR during induction by IRC assessment) and median duration of CR. The median RFS was longer in the quizartinib group (n=147) compared with the placebo group (n=150), 39.3 months versus 13.6 months respectively, as was the median duration of CR (38.6 months versus 12.4 months, respectively).[1, 6]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the exploratory outcomes of the European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) and EuroQol 5-dimension 5-levels (EQ-5D-5L) questionnaires. Assessments were made on day 8 of the first induction cycle and were repeated on day 28 of induction cycles 1 and 2, day 6 and 28 of consolidation cycles 1 to 4, and day 1 of every three cycles during continuation cycles 1 to 34. Baseline scores were comparable between the treatment groups and there were improvements from baseline over the study period in both groups. The results were reported as similar in the treatment groups with the exception of the global health status score and the fatigue score which were numerically better in the placebo group compared with the quizartinib group during the continuation phase of the study.[6, 7]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing quizartinib with midostaurin, the submitting company presented a matching adjusted indirect comparison (MAIC) using the key study for each medicine (QuANTUM-First and RATIFY). Since quizartinib is only licensed for patients with AML with a FLT3-ITD mutation, the subgroup of patients from RATIFY with this mutation was used in the analysis.

Since the study population of RATIFY was aged 18 to 59 years, the subgroup of patients aged <60 years from QuANTUM-First was used.[6, 8] The company also presented an alternative indirect comparison using the multi-level network meta-regression (ML-NMR) approach. This allowed for an indirect comparison with midostaurin to be generated using the full QuANTUM-First study population, not restricted to those aged <60 years. Results from the ML-NMR indicated a lower relative treatment effect for quizartinib than the MAIC results, but this comparison may be considered to better reflect the population for whom treatment may be considered in NHSScotland. The MAIC and ML-NMR address two different groups of people for whom relative effects are estimated: the MAIC considers the QuANTUM-First age-restricted population, whereas the ML-NMR considers a broader population including those aged >60 years. The results of the MAIC were used in the base case of the cost-effectiveness model whilst the results of the ML-NMR were used in a scenario analysis.

Table 2.3: Summary of indirect treatment comparison[6, 8]

Criteria	Overview
Design	MAIC anchored using common control arm of standard chemotherapy alone with matching for platelet count, sex, age and NPM1 mutation status.
Population	Adult patients aged <60 years with newly diagnosed AML with FLT3-ITD mutation.
Comparators	Midostaurin (plus standard chemotherapy)
Studies included	QuANTUM-First (quizartinib versus placebo in combination with standard chemotherapy). RATIFY (midostaurin versus placebo in combination with standard chemotherapy). The MAIC used the subgroup of patients aged <60 years from QuANTUM-First and the FLT3-ITD subgroup from RATIFY.
Outcomes	OS, CR and CIR
Results	In the MAIC for OS and CR, the confidence intervals crossed one, suggesting no evidence of difference between quizartinib and midostaurin. Results of the MAIC of CIR suggested that the risk of relapse was lower with quizartinib than midostaurin.

AML = acute myeloid leukaemia; CI = confidence interval; CR = complete remission; CIR = cumulative incidence of relapse; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OR = odds ratio.

* *MAIC results were considered confidential by the company*

3. Summary of Safety Evidence

At data cut-off (13 August 2021) in QuANTUM-First, the median duration of treatment was 10.7 weeks with quizartinib and 9.5 weeks with placebo. Any treatment-emergent grade 3 or higher adverse event (AE) was reported in 92% versus 90% respectively, with 54% versus 46% of patients reporting a serious AE.[1, 6]

The most frequently reported treatment-emergent AEs of grade 3 or 4 in the quizartinib group versus the placebo group were: febrile neutropenia (43% versus 41%), hypokalaemia (19% versus 16%), neutropenia (18% versus 8.6%), pneumonia (11% versus 11%), thrombocytopenia (7.9% versus 9.7%), decreased neutrophil count (8.7% versus 3.4%) and sepsis (4.2% versus 9.0%)[1, 6]

Prolongation of the QT interval was more frequently reported in the quizartinib than placebo group (14% versus 4.1%) and this was considered treatment-related in 12% versus 3.0% respectively. Most cases in the quizartinib group were manageable with dose modifications and correction of electrolyte imbalances. Two patients in the quizartinib group had a cardiac arrest with ventricular fibrillation on electrocardiogram (ECG).[1, 6]

There were more deaths due to AEs in the quizartinib group (n=30) compared with the placebo group (n=26); mainly due to infection (7.5% versus 4.5%). Four deaths in each treatment group were considered to be due to a treatment-related AE. There was a particular difference between quizartinib and placebo in early deaths (within 60 days of starting treatment: 7.5% versus 4.9%). Older patients and those with poorer ECOG status were more at risk of early death and the SPC recommends close monitoring of elderly patients (aged ≥65 years) for severe infection during induction.[1, 2, 6]

Quizartinib is contraindicated in patients who have congenital long QT syndrome and should not be started in patients if the QTcF interval is > 450 milliseconds. It should be used with caution in patients who are at significant risk of developing QT interval prolongation (those with uncontrolled or significant cardiovascular disease and those receiving concomitant medicines known to prolong the QT interval). The SPC recommends that ECGs should be performed: before starting, once weekly during induction and consolidation, and during the first month following initiation or escalation of maintenance treatment with quizartinib, or more frequently as clinically indicated. More frequent monitoring is recommended in patients at risk of developing QT prolongation and torsade de pointes, including when co-administered with medicines known to prolong the QT interval.[2]

Quizartinib and its active metabolite are primarily metabolised by CYP3A and the SPC provides details of co-administration with medicines which may affect this.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In QuANTUM-First, the addition of quizartinib to standard chemotherapy significantly improved OS in patients with newly diagnosed AML with a FLT3-ITD mutation.[1, 6]
- The improvement in OS was generally consistent across subgroups. In QuANTUM-First, 40% of study patients were aged ≥60 years. The survival benefit of quizartinib over placebo in patients aged ≥60 years was smaller than in younger patients. However, this is the first study to assess the addition of a FLT3 inhibitor to standard chemotherapy in patients ≥60 years..[1, 2, 6, 8] Age would be one of the factors used to determine eligibility for intensive chemotherapy for AML in clinical practice.
- Sensitivity analysis that censored patients who received allogeneic HSCT at any time found a consistent improvement in OS with quizartinib over placebo [6]
- Quizartinib can be used in combination with standard cytarabine and anthracycline induction and is not limited to daunorubicin as an anthracycline, as in the midostaurin marketing authorisation. Quizartinib can be continued as monotherapy for maintenance for up to thirty-six 28-day cycles which is longer than recommended for midostaurin (up to twelve 28-day cycles). In addition, quizartinib can be resumed after an HSCT according to WBC count and at the discretion of the treating physician. It is recommended that midostaurin is stopped 48 hours before the conditioning regimen.[2, 5]

4.2. Key uncertainties

- The difference in OS between the quizartinib and placebo groups statistically favoured quizartinib. However, the Kaplan-Meier survival curves initially favoured placebo until they crossed at approximately 5 months as there were more early deaths within 60 days of starting study treatment in the quizartinib group (7.5%) compared with the placebo group (4.9%). In addition, comparison of the median OS between groups is not informative since the Kaplan-Meier curves appear to plateau around the median. Restricted mean survival time (RMST) differences and landmark analysis at various timepoints have been presented to support the OS results..[1]
- A number of protocol amendments changed the QuANTUM-First study outcomes; change in the primary outcome from EFS to co-primary outcomes of EFS and OS, then in EFS to a secondary outcome with a different definition. The revised definition of EFS as the first secondary outcome (failure to achieve CR within 42 days from the start of the last cycle of induction chemotherapy) failed to reach statistical significance and further testing of secondary outcomes in the hierarchy was not performed. Sensitivity/supplementary analysis of EFS using the original definition (failure to achieve CRc by the end of induction up to day 56), found median EFS was 11.9 months in the quizartinib group and 5.7 months in the placebo group; hazard ratio 0.73 (0.59, 0.90).As detailed in Table 2.2, results for subsequent pharmacodynamic secondary outcomes were similar in both treatment groups and did not support the difference in OS..[1, 6]
- A total of 533 patients received induction therapy, 348 received consolidation therapy and 208 received maintenance therapy. However, the treatment effect of quizartinib was assessed across all phases and it is difficult to determine the effect of each stage of treatment on OS.[1, 6]
- The regulator noted that the safety profile of quizartinib is not negligible. Notably, neutropenia and QT prolongation were more frequently reported treatment-related AEs with quizartinib compared with placebo. Infections were more frequently reported treatment-emergent AEs associated with death as an outcome with quizartinib compared with placebo. Despite this, the addition of quizartinib did not appear to have a detrimental effect on quality of life. However, it is unclear if the safety profile in QuANTUM-First will be generalisable to older, less fit patients in clinical practice.[1, 7]
- There was no direct evidence to compare quizartinib with the relevant comparator midostaurin and the company presented an indirect comparison using two studies, QuANTUM-First and RATIFY. There were a number of limitations with the MAIC including the reduced numbers of patients included in the comparison, the limited matching and remaining heterogeneity. There were differences in the definitions of study outcomes. The cumulative incidence of relapse was derived from a post hoc analysis in QuANTUM-First. The crossing of survival curves in QuANTUM-First may have led to inappropriate assumption of proportional hazards and use of the HR for OS within the MAIC. In order to align with the RATIFY study population, the MAIC was performed in patients aged <60 years but this may affect the generalisability of the MAIC results to patients aged ≥60 years who may be suitable for quizartinib in clinical practice. The submitting company's conclusions of comparable complete

remission rates, reduced risk in OS and significantly reduced risk of relapse with quizartinib compared with midostaurin are uncertain.

4.3. Clinical expert input

Clinical expert consulted by SMC considered that quizartinib provided an alternative to midostaurin in patients with AML with the FLT3-ITD mutation.

4.4. Service implications

Quizartinib is administered orally once daily so there would be no additional service implications to deliver treatment. However, there may be service implications associated with ECG monitoring which is recommended before and during treatment with quizartinib.[2]

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Leukaemia Care and Blood Cancer UK. Both organisations are registered charities.

- Leukaemia Care has received 18.82% pharmaceutical company funding in the past two years, with none from the submitting company. Blood Cancer UK has received 1.6% pharmaceutical company funding in the past two years, with none from the submitting company.

- Acute myeloid leukaemia (AML) is a rapidly progressing condition. Due to the acute nature of the disease, by the time they are diagnosed most patients are already suffering with a severe symptom burden. People are rushed into treatment soon after diagnosis without having time to prepare. They then live with the challenges associated with the disease itself coupled with extensive side effects from intensive treatments which can cause long-term effects. An AML diagnosis can also evoke heightened feelings of anxiety, fear, uncertainty, and a decreased ability to resume social and familial roles. This has a damaging impact on the mental and physical health of patients and their families.

- Quizartinib could help improve survival and quality of life for this group of patients in whom the risk of relapse is higher due to the FLT3 mutations. Patients are likely to welcome this treatment as an option for an illness that is difficult to treat.

- Quizartinib is generally a well-tolerated treatment. Its oral method of administration is also convenient for many patients.

- For this group of patients, having an additional treatment option that may improve their quality and length of life is hugely important for them and their loved ones – who they rely on to provide extensive physical and emotional support.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The company presented an economic case, summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime time horizon of 100 years was used. The mean patient age was 47 years, giving a maximum remaining lifetime of 53 years in the model.
Population	The population was adult patients with newly diagnosed FLT3-ITD positive AML who are eligible to be treated with intensive chemotherapy, consisting of standard cytarabine and anthracycline during induction and standard cytarabine consolidation chemotherapy.
Comparators	Two comparators were used, the midostaurin regimen and the standard chemotherapy regimen. The midostaurin regimen was defined as midostaurin plus chemotherapy in the induction phase, midostaurin plus chemotherapy in the consolidation phase and then midostaurin single-agent maintenance therapy for patients who achieve complete remission but did not receive an HSCT. The standard chemotherapy regimen was defined as chemotherapy in the induction phase, followed by consolidation chemotherapy. SMC clinical experts indicated midostaurin was the comparator most likely to be displaced by quizartinib.
Model description	A Markov model was used. Patients started in the induction phase and could progress to complete remission in first line and through to HSCT in first line. In the first line, transitions to refractory (from induction), relapse (from complete remission) and post-HSCT relapse (from HSCT) were possible. The quizartinib regimen, the midostaurin regimen and the standard chemotherapy regimen were administered in the induction and complete remission in first line health states, with only the quizartinib regimen administered in the HSCT first line state. If relapsing or refractory in the first line, second-line therapies were administered, with second-line health states of complete remission, HSCT, post-HSCT maintenance, and relapse. Risk of death was possible from all health states. A 28-day model cycle was used.
Clinical data	Clinical data were sourced from the QuANTUM-First adjusted population, results of the MAIC, and published literature.[9, 10] The QuANTUM-First patient population was reweighted in the MAIC to obtain the QuANTUM-First adjusted population (effectively a RATIFY-like QuANTUM-First population). Individual patient level data were then obtained, including but not limited to, relapse after composite complete remission (censored at the start date of all HSCT), survival after composite complete remission (censored at the start date of all HSCT and relapse), relapse from protocol-specified HSCT, and survival from protocol-specified HSCT (censored at relapse). MAIC odds ratio and hazard ratio results were used in the model. These were the complete remission odds ratio of quizartinib versus midostaurin, the cumulative incidence of relapse hazard ratio of quizartinib versus placebo, the cumulative incidence of relapse hazard ratio of quizartinib versus midostaurin, the overall survival hazard ratio of quizartinib versus placebo, and the overall survival hazard ratio of quizartinib versus midostaurin. For the quizartinib regimen and standard chemotherapy regimen the mean treatment duration from the QuANTUM-First study was applied in the model based on a health-state occupancy approach, also utilising duration caps. For the midostaurin regimen, induction and consolidation treatment time were assumed identical to the quizartinib regimen, with the maintenance treatment duration sourced from the midostaurin SmPC.

Extrapolation	A set of time-invariant and time-variant transition probabilities was applied to extrapolate outcomes for each treatment arm in each model transition. In general, in the first line health states, the adjusted QuANTUM-First data were used to derive per cycle time-invariant or time-variant (extrapolated using the log-normal distribution) transition probabilities in the quizartinib regimen and standard chemotherapy regimen arms, with transition probabilities in the midostaurin regimen arm derived from applying the outputs of the MAIC. There were exceptions, with MAIC outputs occasionally applied in the standard chemotherapy arm to extrapolate outcomes, such the transition from complete remission in first line to relapse in first line, which used the cumulative incidence of relapse hazard ratio of quizartinib versus placebo. In the second-line health states, published literature was used to derive the time-invariant transition probabilities for each treatment arm. A functional cure assumption was included in the model and was applied in the complete remission in first line or HSCT in first line health states beyond 3 years, with no probability of relapse from this point. A two-fold mortality ratio was assumed applied to background mortality to calculate the post-cure mortality.
Quality of life	Health state utility values were sourced from the literature.[11-13] In the first line health states utility values ranged from 0.530 in the refractory health state to 0.830 in the complete remission health state. Health state utility values in second-line health states were assumed to be 90% of their respective first line health state utility values. Utility values once functional cure was achieved were assumed to be those of the general population.[14] Except for a graft versus host disease disutility (0.173), adverse event disutilities were not included, as these were assumed captured in the health state utility values. Utility values were adjusted for age.
Costs and resource use	Costs included in the model were medicine acquisition, subsequent treatments, administration, treatment monitoring, disease management, adverse events, end of life costs, and the cost of an HSCT.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for the comparator medicine of midostaurin and subsequent treatment medicine of gilteritinib and these were included in the results used for decision-making by using estimates of the comparator PAS price. The results presented do not take account of the PAS for midostaurin or gilteritinib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for midostaurin and gilteritinib due to commercial confidentiality and competition law issues.

6.2. Results

The base case results are shown in the table below. These results include the quizartinib PAS discount only.

Table 6.2: Base case results (quizartinib PAS)

	ICER (£/QALY)
Quizartinib regimen	-
Midostaurin regimen	Dominant
Standard chemotherapy regimen	5,144

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.

Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.3. Sensitivity analyses

Key scenario analysis results are shown in Table 6.3. The most impactful scenarios were those that varied the cumulative incidence of relapse hazard ratios from the MAIC, used the multilevel network meta-regression (ML-NMR) instead of MAIC for the indirect treatment comparison, and used a trial-based analysis instead of the base case approach to compare the quizartinib regimen to the standard chemotherapy regimen. These results included the quizartinib PAS discount only.

Table 6.3: Scenario analysis results (quizartinib PAS)

				Versus midostaurin regimen	**Versus standard chemotherapy regimen**
	Parameter	**Base case**	**Scenario**	**ICER (£/QALY)**	**ICER (£/QALY)**
	Base case			**Dominant**	**5,144**
1	Extrapolation - Relapse from CRc for quizartinib	Log-normal	Exponential	Dominant	5,397
2	Extrapolation - Death from CRc for quizartinib	Log-normal	Exponential	Dominant	5,334
3	Extrapolation - Death from protocol-specified HSCT 1L for quizartinib and SC	Log-normal	Gen. Gamma	Dominant	5,160
4	Extrapolation - Relapse from protocol-specified HSCT 1L for quizartinib and SC	Log-normal	Gen. Gamma	Dominant	5,431
5a	Cumulative incidence of relapse hazard ratio of quizartinib vs placebo	Point estimate	Lower bound	Dominant	3,286
5b			Upper bound	Dominant	9,211
6a	Cumulative incidence of relapse hazard ratio of quizartinib vs midostaurin	Point estimate	Lower bound	Dominant	5,144
6b			Upper bound	Dominant	5,144
7a	OS Hazard ratio: quizartinib vs midostaurin	Point estimate	Lower bound	Dominant	5,144
7b			Equivalent (HR=1)	Dominant	5,144
7c			Upper bound	Dominant	5,144
8a	OS hazard ratio quizartinib vs placebo	Point estimate	Lower bound	Dominant	5,298
8b			Upper bound	Dominant	5,039

9a	CR Odds ratio: quizartinib vs midostaurin	Point estimate	Lower bound	Dominant	5,144
9b			Equivalent (OR=1)	Dominant	5,144
9c			Upper bound	Dominant	5,144
10	ITC approach	MAIC	ML-NMR	Dominant	14,334
11	Utility values	Literature	QuANTUM-First and literature	Dominant	5,084
12	Cure point	3 years	5 years	Dominant	6,013
13	QuANTUM-First trial-based analyses	Base case	Trial-based analysis	NA	33,499
14	Combine (7b, 8b, 9b)		No evidence of difference in OS or complete response	Dominant	5,039
15	Combine (5b,6b,7c,8b,9a)		Conservative bounds of MAIC	Dominant	9,503

Abbreviations: 1L = first line; CR = complete remission; CRc = Composite complete remission; HSCT = Allogeneic haematopoietic cell transplantation; ICER = incremental cost-effectiveness ratio; ITC: Indirect treatment comparison; LYG = life years gained; MAIC = matching adjusted indirect comparison; ML-NMR = multilevel network meta-regression; NA = not applicable; OS: overall survival; QALYs = quality-adjusted life years.

Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.4. Key strengths

- A comprehensive selection of parameters was considered in one-way deterministic scenario analysis. These were varied through an appropriate range.
- The company presented a comprehensive model structure for modelling disease progression for patients receiving treatment for newly diagnosed AML.

6.5. Key uncertainties

- There were uncertainties in the MAIC. These included restricting the population of the QuANTUM-First study to a subgroup of patients less than 60 years old to match the RATIFY study population, and wide confidence intervals for the overall survival, complete remission and cumulative incidence of relapse results. The bounds of all MAIC results used in the economic evaluation were explored in scenario analyses (scenarios 5 to 9), highlighting sensitivity in the base case economic results to these parameters. In addition, an alternative indirect treatment comparison approach was considered as a scenario, the ML-NMR (scenario 10). 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. The ML-NMR analysis is therefore not restricted to the age

criteria restriction in the RATIFY study and can consider patients aged over 60 years old to provide results in a non-restricted population. Given this, the approach may better reflect the population for whom treatment may be considered in NHSScotland practice. However, there are statistical assumptions and complexities of this relatively new methodology. The results indicated a lower estimate of the treatment effect than the MAIC. A further scenario analysis was available that considered a trial-based analysis (scenario 13). This estimated the cost- effectiveness of quizartinib based only on head-to-head data from the QuANTUM-First trial, fitting independent extrapolations to relevant data in both arms, with no reference to MAIC results. The estimated treatment effect was reduced in this scenario.

- There were uncertainties in the direct head-to-head overall survival evidence of quizartinib versus placebo from QuANTUM-First. Alternative extrapolations and variation in the MAIC survival hazards ratios for quizartinib versus placebo showed a limited impact on economic results in scenario analyses (scenarios 2, 3, and 8).
- The applied functional cure, whilst viewed as reasonable by SMC clinical experts, required assumptions of the time point of implementation, effect on background mortality, and the assigned utility values. The 3-year time point was chosen to align with the OS in QuANTUM-First flattening, consistency with prior SMC appraisals in AML (SMC2252 and SMC1330/18) and clinical expert opinion obtained by the submitting company. However, selected SMC clinical experts highlighted a 5-year timepoint as an alternative (scenario 12). In addition, utility values were assumed to revert to the general population for the cured population. The submitting company provided a supplementary scenario removing this consideration, with a limited impact on economic results.
- There was uncertainty in the utility values. The submitting company noted that as the QuANTUM-First study was not designed to formally compare treatment impact of quizartinib to placebo on patient HRQoL and no long-term data collection was performed, the utility values were drawn from literature in prior published cost-effectiveness studies for untreated AML. However, a scenario applying QuANTUM-First utility values showed a small impact on economic results (scenario 11), with utility values also not identified as sensitive parameters in one-way deterministic sensitivity analysis.

7. Conclusion

After considering all the available evidence, the Committee accepted quizartinib for use in NHSScotland.

8. Guidelines and Protocols

The European LeukemiaNET (ELN) published “diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN” in 2022.[15]

The European Society of Medical Oncology published “acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up” in 2020.[16]

9. Additional Information

9.1. Product availability date

01 July 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (28 days) (£)
Quizartinib	**Induction (up to 2 cycles): 35.4 mg orally daily for 14 days in each cycle**	**6,451**
	Consolidation (up to 4 cycles): 35.4 mg orally daily for 14 days in each cycle	**6,451**
	Maintenance (up to 36 cycles): 26.5 mg orally daily for 14 days then 53 mg orally daily if QTcF ≤450 milliseconds	**cycle 1: 6,451 to 9676 Subsequent cycles: 6,451 to 12,902**

Costs from BNF online on 5 August 2024. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

The SMC clinical expert responses indicate patient numbers are likely to be higher than estimated by the submitting company.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 13 September 2024.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.