Medicinrådet

Bilag til Medicinrådets vurdering af Quizartinib til behandling af akut myeloid leukæmi

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. Quizartinib til behandling af akut myeloid leukæmi.
2. Ansøgers endelige ansøgning vedr. Quizartinib til behandling af akut myeloid leukæmi.

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12.01.2026

MBA/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.02.2026
Leverandør	Daiichi-Sankyo
Lægemiddel	Vanflyta (quizartinib)
Ansøgt indikation	FLT3-ITD-positiv nydiagnosticeret akut myeloid leukæmi
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Vanflyta (quizartinib):

Tabel 1: Forhandlingsresultat, betinget pristilbud:

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Vanflyta	17,7 mg (28 stk. filmovertrukne tabl.)	51.203,00	[redacted]	[redacted]
Vanflyta	26,5 mg (56 stk. filmovertrukne tabl.)	102.407,00	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Vanflyta, indkøbes lægemidlet til nedenstående og ubetingede priser.

Tabel 2: Forhandlingsresultat, ubetinget pristilbud:

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Vanflyta	17,7 mg 28 stk. filmovertrukne tabl.	51.203,00	[redacted]	[redacted]
Vanflyta	26,5 mg 56 stk. filmovertrukne tabl.	102.407,00	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

[redacted]

Tabel 3 viser lægemiddeludgifter for Vanflyta og Rydapt.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Opstartsår:				
Vanflyta (Induktion og konsolidering)	17,7 mg, (28 stk. filmovertrukne tabl.)	**Induktionsfasen:** Cyklus 1 og 2: 35,4 mg én gang dagligt fra dag 8 til 21 **Konsolideringsfasen** Cyklus 3-6: 35,4 mg én gang dagligt fra dag 6 til 19.	[redacted]	[redacted]
Vanflyta (vedligeholdelse)	26,5 mg, (56 stk. filmovertrukne tabl.)	Startdosis: 26,5 mg én gang dagligt i 2 uger, forudsat QTcF ≤ 450 ms. Efter to uger, hvis QTcF fortsat ≤ 450 ms, øges dosis til 53 mg én gang dagligt og uden pause mellem cyklerne.	[redacted]	
Rydapt (midostaurin) (Induktion- & konsolidering)	25 mg, (112 stk., kapsler, bløde)	**Induktionsfasen:** Cyklus 1 og 2: 50 mg to gange dagligt fra dag 8 til 21. **Konsolideringsfasen** Cyklus 3-6: 50 mg én gang dagligt fra dag 8 til 21.	[redacted]	[redacted]
Rydapt (midostaurin) (vedligeholdelse)	25 mg, (112 stk., kapsler, bløde)	Cyklus 7-13: 50 mg to gange dagligt.		
Vedligeholdelsesår:				
Vanflyta	26,5 mg, (56 stk. filmovertrukne tabl.)	Cyklus 14-26: 53 mg én gang dagligt og uden pause mellem cyklerne.	[redacted]	[redacted]
Rydapt (midostaurin)	25 mg, (112 stk., kapsler, bløde)	Cyklus 14-15: 50 mg to gange dagligt.	[redacted]	[redacted]

*Én cyklus er 28 dage. De beskrevne doseringer er fuld dosering jf. Medicinrådets vurderingsrapport. I vedligeholdelsesfasen kan der behandles med Vanflyta i op til ca. 33 måneder svarende til 36 cykler og med Rydapt op til 8 måneder svarende til 8,69 cykler

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of Vanflyta® for the treatment of FLT3-ITD positive newly diagnosed acute myeloid leukaemia

Contact information

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Color scheme for text redaction	
Color of redacted text	**Definition of redacted text**
	Confidential information

Table of contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike Information Criteria
AIP	Apotekernes indkøbspris
ALL	Acute Lymphocytic Leukaemia
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukaemia
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
ATC	Anatomical Therapeutic Chemical
AZCERT	The Arizona Center for Education and Research on Therapeutics
BIC	Bayesian Information Criterion
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CE-marked	Conformité Européenne-marked
Chemo	Chemotherapy
CI	Confidence interval
CIR	Cumulative incidence of relapse
CNS	Central nervous system
CR	Complete remission
CRc	Composite complete remission
CRi	Complete remission with incomplete neutrophil or platelet recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DFS	Disease-free survival
DK	Denmark
DKK	Danish crown
DMC	Danish Medicines Council
DSE	Daiichi Sankyo Europe
DRG	Diagnosis related group
DSU	Decision Support Unit
DoCR	Duration of complete remission
EBMT	European Society for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EED	Economic evaluation database
EFS	Event-free survival
EHA	European Haematology Association
ELN	European Leukemia Net
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer core quality of life questionnaire
EQ-5D	EuroQoL five dimensions
EQ-5D-3L	EuroQoL five dimensions three levels
EQ-5D-5L	EuroQoL five dimensions five levels
ER	Emergency room
ERG	Evidence review group
ES	Effect size
ESMO	European Society For Medical Oncology
ESS	Estimated sample size
EU	European Union
FACT-Leu	Functional Assessment of Cancer Therapy-Leukaemia
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GP	General practitioner
GVHD	Graft-vs.-host disease
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HSCT	Allogeneic haematopoietic stem cell transplantation
HSUV	Health state utility values
HTA	Health technology assessment
HUI	Health utility index
INAHTA	International Network of Agencies for Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IPD	Individual patient data
IQR	Interquartile range
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITD	Internal tandem duplication
ITT	Intention-to-treat
IV	Intravenous
IVD	In vitro diagnostic
JMDsole	Juxtamembrane domain
JMD/TKD1	Juxtamembrane domain and tyrosine kinase domain-1
KM	Kaplan-Meier
KOL	Key opinion leader
LS	Least squares
LY	Life year

LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MAR	Missing-at-random
MMRM	Mixed-effects model for repeated measures
MRD	Minimal residual disease
MS	Millisecond
N/A	Not available
NCI	National Cancer Institute
ND	Newly-diagnosed
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NORDCAN	Association of Nordic Cancer Registries
NPM1	Nucleophosmin 1
NR	Not reached
N/A	Not applicable
OR	Odds ratio
OS	Overall survival
PCB	Placebo
PH	Proportional hazards
PICOS	Population, intervention, comparator, outcome, and study design
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
Q-F	QuANTUM-First quizartinib clinical study
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
RCT	Randomised controlled trial
RDI	Relative dose intensity
RFS	Relapse-free survival
RNA	Ribonucleic acid
r/r	Relapsed or refractory
RWE	Real world evidence
SAE	Serious adverse event
SAGO	Scientific advise group - oncology
SCT	Stem cell transplantation
SC	Standard chemotherapy
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TA	Technology assessment
TEAE	Treatment-emergent adverse event
TEM	Treatment-effect modifier
TKD	Tyrosine kinase domain
TKD1sole	Tyrosine kinase domain-1

TSD	Technical support document
TP	Transition probability
UK	United Kingdom
ULN	Upper limit of normal
UNS	Uden nærmere specifikation
US	United States
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization
1L	First-line
2L	Second-line

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Vanflyta®
Generic name	Quizartinib
Therapeutic indication as defined by EMA	Quizartinib is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by quizartinib single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) positive.
Marketing authorization holder in Denmark	Daiichi Sankyo Nordics ApS Amagerfælledvej 106, 2. 2300 Copenhagen S Phone +49 89 78080 www.daiichi-sankyo.dk info@daiichi-sankyo.dk
ATC code	L01EX11
Combination therapy and/or co-medication	Induction chemotherapy: cytarabine and anthracycline Consolidation chemotherapy: cytarabine Maintenance: none
Date of EC approval	21st of November 2023
Has the pharmaceutical received a conditional marketing authorisation?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the Danish Medicines Council (DMC) (yes/no)	None
Dispensing group	BEGR/NBS

Overview of the pharmaceutical	
Packaging – types, sizes/number of units and concentrations	Vanflyta (quizartinib) 17.7 mg, 28 film-coated tablets Vanflyta (quizartinib) 26.5 mg, 56 film-coated tablets

Source: European Medicines Agency, 2023 (1).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Quizartinib in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed as single agent maintenance therapy for adult patients with newly diagnosed AML that is *FLT3*-ITD positive.
Dosage regiment and administration	**Induction**: Cycle 1, 28-days: 35.4 mg (2 × 17.7 mg) orally once daily on days 8-21. Cycle 2, 28-days: 35.4 mg (2 × 17.7 mg) orally once daily on days 8-21 or days 6-19 as optional second induction. **Consolidation**: 35.4 mg (2 × 17.7 mg) orally once daily on days 6 to 19 for up to four 28-day cycles. **Maintenance**: Starting dose of 26.5 mg orally once daily for two weeks if the QT interval corrected by Fridericia's formula (QTcF) is ≤ 450 ms. After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg (2 × 26.5 mg) once daily. Single-agent maintenance therapy may be continued for up to thirty-six 28-day cycles.
Choice of comparator	Midostaurin
Prognosis with current treatment (comparator)	*FLT3*-ITD AML is a rapidly progressive cancer leading to a decrease in life expectancy. In the RATIFY study, median overall survival (OS) was 74.7 months for midostaurin (95% CI: 31.5, NE) and 25.6 months for Standard Chemotherapy (SC) (95% CI 18.6, 42.9) (2).
Type of evidence for the clinical evaluation	Matching adjusted indirect comparison (MAIC)
Most important efficacy endpoints (Difference/gain compared to comparator)	**QuANTUM-First (Q-F)** The median OS was NE (95% CI: NE, NE) in the quizartinib arm and 23.0 months (95% CI: 13, NE) in the placebo arm. Quizartinib showed statistically significant OS benefit compared with placebo (HR 0.684 (0.493, 0.949). The rate of CRc was [redacted]% (95% CI: [redacted] – [redacted]) and [redacted]% (95% CI: [redacted] – [redacted]) in the quizartinib and placebo arm respectively. CIR rate at 24 months was 22.6% (95% CI: 14.1 – 32.4) and 37.8 (95% CI: 27.2 – 48.3) for quizartinib and placebo respectively **RATIFY:** The median OS was 74.7 months (95% CI: 31.5, NE) in the midostaurin arm and 25.6 months (95% CI: 18.6, 42.9) in the placebo arm. The rate of CR was 58.9% (95% CI 53.6, 64.0) in the midostaurin group and 53.5% (95% CI 48.2, 58.8) in the placebo group
Most important serious adverse events (SAEs) for the intervention and comparator	In the Q-F <60 population febrile neutropenia, pneumonia and sepsis were the most common SAE, reported in [redacted]%, [redacted]% and [redacted]% of the quizartinib arm and in [redacted]%, [redacted]% and [redacted] in the placebo arm, respectively. In RATIFY, decreased haemoglobin, neutrophil count, and platelet count were the most common SAE reported in 43.3%,

Summary	
	40.85%, and 43.66% for midostaurin and 41.81%, 41.24%, and 41.24% for placebo.
Impact on health-related quality of life (HRQoL)	EQ-5D-5L DK index score based on Q-F was used to measure HRQoL. Mixed-effects model for repeated measures (MMRM): No meaningful difference in EQ-5D-5L score was observed between quizartinib and placebo, with a least-squares mean difference of [redacted] (95% CI [redacted], [redacted]) in the ITT population and of [redacted] (95% CI [redacted], [redacted]) in the Q-F population < 60 years of age. No direct comparison was available for quizartinib vs midostaurin.
Type of economic analysis that is submitted	Cost-utility analysis based on a semi-Markov model.
Data sources used to model the clinical effects	Quizartinib: Q-F data for the population <60 adjusted to the RATIFY population through MAIC. Scenario based on Q-F ITT population provided in the appendix. Midostaurin: MAIC and published RATIFY trial data (2, 3)
Data sources used to model the health-related quality of life	Overall health state EQ-5D-5L DK index score from Q-F (ITT population) applied while on 1L treatment and in the relapse health states. Health state following 1L treatments: utility values sourced from NICE TA523 (4).
Life years gained	[redacted] years
QALYs gained	[redacted] QALY
Incremental costs	[redacted] DKK
ICER (DKK/QALY)	[redacted] DKK/QALY
Uncertainty associated with the ICER estimate	The main uncertainty of the health economic analysis derives from the lack of head-to-head comparison with midostaurin and the use of MAIC to estimate comparative effectiveness.
Number of eligible patients in Denmark	Incidence: 2023: 31; 2024: 31; 2025: 32; 2026: 32; 2027: 32 Prevalence: 2023: 200; 2024: 201; 2025: 202; 2026: 203; 2027: 204 (see section 3.2 and 13 for assumption behind estimates).
Budget impact (in year 5)	The budget impact (undiscounted) in year 5 is [redacted] DKK.

Source: European Medicines Agency, 2023 (1); Julisson et al., 2020 (5); Daiichi Sankyo, 2022(6-8); ClinicalTrials.gov, 2008 (9); Erba et al 2023 (10); Stone et al, 2017 (2); NORDCAN, 2024 2021 (11, 12).

3. The patient population, intervention, choice of comparator and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

AML is a rapidly progressing cancer of the myeloid blasts (13, 14). It involves a maturation arrest of bone marrow cells, leading to two main issues: decreased production of normal blood cells (causing anemia, thrombocytopenia, and neutropenia) and the rapid proliferation and reduced apoptosis of abnormal myeloblasts, which accumulate in the bone

marrow, blood, and sometimes the liver and spleen (15). AML is heterogeneous, classified into secondary, treatment-related, and de novo subtypes, with the latter occurring in previously healthy individuals, without a prior history of myeloid disease or known exposure to potential leukemogenic therapy or agents (13, 16, 17) . Around 33% of AML patients have an FLT3 mutation (~25% with ITDs and ~7-10% with TKD mutations). The *FLT3* gene encodes a tyrosine kinase receptor, which plays a key role in haematopoiesis (18). The *FLT3*-ITD mutation leads to constitutive activation of the tyrosine kinase receptor and downstream signalling through RAS/RAF/MEK/ERK kinases, STAT5, and PI3-kinases (19).

3.1.2 Clinical presentation and symptoms of the condition

Most of the AML clinical manifestations are related to the accumulation of malignant myeloid cells within the bone marrow, peripheral blood, and (less commonly) other organs (13). Patients typically present with a combination of leucocytosis and signs of bone marrow failure, such as anaemia and thrombocytopenia (13). General symptoms include: frequent infection; tiredness and fatigue; weakness; shortness of breath; fever; easy bruising or bleeding; petechiae; pale skin; night sweats; bone or joint pain; swollen or sore glands in the neck, armpit, or groin; loss of appetite or weight loss; fullness or discomfort in stomach or abdomen; and symptoms of anaemia (20). Symptoms usually develop four to six weeks before diagnosis and increase in severity over time (14). Serious, potentially life-threating complications of AML includes uncontrolled infections; bleeding in the lungs, gastrointestinal tract, and central nervous system; and leukostasis (15, 20). Patients with *FLT3-ITD+* AML have a higher rate of leucocytosis and a higher blast burden than patients with *FLT3*-ITD negative AML (21).

3.1.3 Prognosis

Overall, the outcome of patients with AML is poor, with a 5-year survival rate of 40%, which rapidly declines with increasing age at diagnoses (22). The presence of an *FLT3*-ITD+ confers an unfavourable prognosis, with relapse being the principal cause of treatment failure for most of these patients. On average, the median time to relapse for patients with *FLT3*-ITD+ AML in first remission was 9 months (21, 23, 24). An analysis conducted on the Swedish AML registry data (2007-2019) resulted in median OS of 1.87 years for patients <60 years with *FLT3*-ITD compared with >8 years for patients <60 years without *FLT3*-ITD (P = 0.00008) (5). In a DMC assessment from 2022 of gilteritinib for the treatment of patients with relapsed or refractory (r/r) AML with *FLT3* mutation, the DMC states that the current curative treatment results in an expected 5-year survival in approximately 25-30% of patients under 60 years of age with *FLT3* mutations, and that the survival depends on the cytogenetically defined prognostic subgroup as well as age, comorbidity, and performance status at disease onset (25). The prognosis with current treatment options is described further in section 3.3.2.

3.1.4 Patients' functioning and health-related quality of life

There is limited information on quality of life among patients with *FLT3-ITD+*AML. In a cross-sectional survey conducted in 2015, 82 patients with either newly diagnosed or r/r AML were evaluated; among these patients, 54 had molecular testing and 7 patients tested positive for the *FLT3*-ITD mutation (26). Results suggested that patients with *FLT3-ITD+* AML have worse health-related quality-of-life (HRQoL) compared to patients without the mutation, as measured by the EQ-5D-3L and Functional Assessment of Cancer Therapy-Leukaemia (FACT-Leu). The EQ-5D visual analogue scale (VAS) scores were 47.6 versus

63.7 (*P* = 0.0428; effect size [ES] = 0.816). The EQ-5D utility scores were 0.64 versus 0.76 (*P* = 0.1629; ES = 0.568). The overall FACT-Leu scores were 85.5 versus 100 (*P* = 0.1484; ES = 0.588).

3.2 Patient population

As stated in section 3.1.3, the survival among patients with AML depends on the cytogenetically defined prognostic subgroup as well as age, comorbidity, and performance status at disease onset. The distribution of these factors among Danish patients with AML or acute lymphocytic leukaemia (ALL) in 2022 was reported in the Danish acute leukemia database and myelodysplastic syndrome database yearly report (27). AML and ALL patients were reported to have a median age of 72 years. The 25th to 75th percentile of the population fell between 59 and 80 years. The youngest 5% were below 36 years and the oldest 5% above 87 years. 48.55% had no comorbidities (score 0), 32.78% had mild to moderate comorbidities (score 1–2), and 18.67% had severe comorbidities (score ≥3). Most individuals (91.29%) had a WHO performance score of 0–2, indicating good functional status, while 8.71% had a score of 3–4, reflecting poorer functional status. **7.73%** were classified as low risk, **45.89%** as intermediate risk, and **12.08%** as high risk. Additionally, **34.3%** fell into categories of ALL, myelodysplastic syndromes, or unspecified/unknown risk (27).

The incidence and prevalence of AML in Denmark are reported by NORDCAN. The incidence rate is **3.0 per 100,000** inhabitants for 2021 (11). The prevalence rate was **19.3 per 100,000** inhabitants for 2021 (12). The frequency of *FLT3-ITD+* mutation among patients with AML is expected to be **25%** (18). The incidence and prevalence of *FLT3*-ITD AML were estimated using the total Danish population for 2019-2023 reported by Statistic Denmark (28).

Table 1 Incidence and prevalence in the past five years (*FLT3-ITD+* AML)

Year	2019	2020	2021	2022	2023
Incidence in Denmark	44	44	44	44	44
Prevalence in Denmark	280	281	282	283	286
Global prevalence *	N/A	N/A	N/A	N/A	N/A

Notes: the total population used was 5806081 for 2019, 5822763 for 2020, 5840045 for 2021, 5873420 for 2022 and 5932654 for 2023.
Source: NORDCAN, 2023 (11), (12), Yu et al. 2020 (18); DMCG and RKKP, 2024 (29); Hellesøy et al., 2021 (30); Statistics Denmark, 2024 (28).

It can be assumed that **100%** of patients with AML are tested for FLT3-ITD mutations status, as it is recommended in Danish clinical treatment guidelines (29, 30). Furthermore, **70%** of age suitable patients can be considered eligible for intensive chemotherapy, according to what estimated in the NICE TA 523 and validated with Danish clinicians (31, 32).

The estimated number of patients eligible for treatment with quizartinib (Table 2) were estimated based on a total Danish population of 5,989,985 in 2024 (28), and applying an annual population growth of 0.48% for the subsequent years (28).

Table 2 Estimated number of patients eligible for treatment

Year	2025	2026	2027	2028	2029
Number of patients in Denmark who are eligible for treatment in the coming years	31	32	32	32	32

Source: NORDCAN, 2023 (11); Yu et al. 2020 (18); DMCG and RKKP, 2024 (29); Hellesøy et al., 2021 (30); Statistics Denmark, 2024 (28); National Institute for Health and Care Excellence, 2017 (31).

3.3 Current treatment options

3.3.1 Current treatment options

In Denmark, patients are treated based on one of four principles: intensive treatment, semi-intensive treatment, low-intensive treatment, or supportive treatment. In the following, intensive treatment is described (29) in alignment with the indication relevant for this submission. The induction treatment consists of two courses. The first induction course ("3+10") consists of 100 mg/m^2 cytarabine administered intravenous (IV) twice daily for 10 days combined with 60 mg/m^2 daunorubicin administered IV once daily for 3 days. It is possible to supplement this treatment with 3 mg/m^2 (maximum 5 mg) gemtuzumab ozogamicin in accordance with the MRC regime (first induction course: day 1 and 4 or 4 and 7). The reinduction course ("3+8") consists of 50 mg/m^2 daunorubicin IV once daily for 3 days combined with 100 mg/m^2 cytarabine IV twice daily for 8 days. Midostaurin 50 mg should be administered twice daily for 14 days from 2 days after ended induction treatment (29). Patients 60 years of age or younger should go through two consolidation courses consisting of 3 g/m^2 cytarabine IV administered 6 times every 12 hours over 3 days. Patients older than 60 years of age should go through one consolidation course consisting of 1,5-2 g/m^2 cytarabine IV administered 6 times every 12 hours over 3 days. Midostaurin 50 mg should be administered twice daily for 14 days from 2 days after ended consolidation treatment (29). Consolidation can be conducted through allogeneic stem cell transplantation, when 400-800 mg sorafenib should be administered daily as maintenance treatment for two years (29). As maintenance treatment midostaurin 50 mg should be administered twice daily for 12 months after ended treatment (29).

3.3.2 Expected prognosis

Midostaurin combined with SC showed a benefit in OS for TKD and ITD high/low AML vs SC (hazard ratios [HR]s of 0.65 and 0.80 to 0.81, respectively), in a FLT3+ AML population between 18-59 years. Additionally, the rate of CIR with midostaurin was reported to be approximately 40% at 2 years of follow-up (2).

3.4 The intervention

In Table 3, key descriptive information of quizartinib is presented and following the table, the mechanism of action of quizartinib is described.

Table 3 Key descriptive information of quizartinib

Overview of intervention	
Therapeutic indication relevant for the assessment	In combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by single-agent maintenance therapy for adult patients with newly diagnosed FLT3-ITD + AML.
Method of administration	Oral administration

Overview of intervention	
Dosing	**Induction**: Cycle 1, 28-days: 35.4 mg (2 × 17.7 mg) once daily on days 8-21. Cycle 2, 28-days: 35.4 mg (2 × 17.7 mg) once daily on days 8-21 or days 6-19 as optional second induction. **Consolidation**: 35.4 mg (2 × 17.7 mg) once daily on days 6 to 19 for up to four 28-day cycles. **Maintenance**: Starting dose of 26.5 mg once daily for two weeks if QTcF is ≤ 450 ms. After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg (2 × 26.5 mg) once daily. Single-agent maintenance therapy may be continued for up to 36 28-day cycles.
Dosing in the health economic model (including relative dose intensity [RDI])	As above and applying a [redacted] RDI, corresponding to the mean RDI overall for the safety analysis set* (8). The RDI was derived from the mean RDI across trial period, calculated dose intensity/planned dose intensity × 100. RDI is further described in section 11.1
Should the pharmaceutical be administered with other medicines?	**Standard chemotherapy : Induction:** Cycle 1: 7 + 3 (cytarabine [100 or 200 mg/m^2/day] IV on days 1 through 8 + daunorubicin [60 mg/m^2/day] IV or idarubicin [12 mg/m^2/day] IV on days 1-3). Cycle 2: Optional second induction (7 + 3 or 5 + 2 [5 days cytarabine IV + 2 days daunorubicin IV or idarubicin IV]). **Consolidation**: High-dose cytarabine (1.5-3 g/m^2 every 12 hours on days 1, 3, and 5) for up to 4 cycles and/or allogeneic haematopoietic stem cell transplantation (HSCT). Cytarabine among subjects <60 years old: 3.0 g/m^2 IV infusion, every 12 hours. Cytarabine among subjects ≥60 years old: 1.5 g/m^2 IV infusion, every 12 hours. **Maintenance:** None. Prophylactic antiemetics should be administered in accordance with local medical practice as per patient tolerance.
Treatment duration / criteria for end of treatment	In all phases, each cycle should be 28 days in duration. Additional time is allowed for recovery of blood counts in the induction or consolidation phases, if needed. The total duration of treatment with study drug should be up to 42 cycles (inclusive of induction, consolidation, and maintenance phases).
Necessary monitoring, both during administration and during the treatment period	Blood tests: Regular blood tests during treatment with quizartinib to check blood cells (white blood cells, red blood cells, and platelets) and electrolytes (salts such as sodium, potassium, magnesium, calcium, chloride and bicarbonate in blood). Electrolytes should be checked more often if the patient experience diarrhoea or vomiting. Electrocardiogram (ECG): Before and during treatment, ECGs will be done weekly initially and less often thereafter. ECGs will be performed more often if the patient is taking other medicines that prolong the QT interval. Patients older than 65 years of age should be closely monitored for the occurrence of severe infections during induction.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	*FLT3-ITD+* confirmation using a Conformité Européenne-marked (CE-marked) in vitro diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, confirmation of *FLT3-ITD+* AML should be assessed by an alternate validated test.
Package size(s)	28 x 18 mg tablets 56 x 27 mg tablets

Sources: European Medicines Agency, 2023 (1); Daiichi Sankyo, Inc., 2022 (8); Daiichi Sankyo, Inc., 2023 (33).

3.4.1 Description of Mode of Action

Quizartinib is an inhibitor of the receptor tyrosine kinase *FLT3*. Quizartinib and its major metabolite AC886 competitively bind to the adenosine triphosphate binding pocket of the inactive conformation of *FLT3* with high affinity. Quizartinib and AC886 inhibit *FLT3* kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream *FLT3* receptor signalling leading to potent antiproliferative activity, induction of apoptosis, and rapid clearance of leukemic blast from peripheral blood, as well as induction of cellular differentiation of bone marrow blasts, and thus blocking *FLT3*-ITD dependent cell proliferation (34-42).

3.4.2 The intervention in relation to Danish clinical practice

Quizartinib is expected to be used during the induction, consolidation, and maintenance phase replacing the use of midostaurin among *FLT3-ITD+* patients. It is expected that Danish clinical practice will be altered, as some *FLT3-ITD+* patients will receive quizartinib instead of midostaurin. SC administered in induction and consolidation phases is not expected to vary after the introduction of quizartinib in the treatment pathway.

Danish clinical experts underlined that despite age being an important patient characteristic, the treatment pathway in clinical practice is mostly influenced by the patient overall performance status. In addition, the experts consulted recognised that the slight differences in SC dosing schedule described in the clinical guideline (reported in section 3.3.1) and the one specified in Q-F (reported in Table 3), are not expected to alter the overall efficacy of the treatments (29, 32)

3.5 Choice of comparator(s)

Midostaurin was identified as relevant comparator for the treatment of de novo FLT3-ITD+ AML patients through the review of the Danish treatment guideline (29) as described in sections 3.3 and 3.4 and confirmed by Danish KOL.

No head-to-head trial was available comparing quizartinib and midostaurin.

As placebo plus SC served as common comparator across Q-F and RATIFY, an indirect treatment comparison (ITC) was conducted to estimate the relative efficacy of quizartinib versus midostaurin (described in section 6.1.5.4). The key descriptive information for midostaurin and the RATIFY trial are described in Table 4.

Table 4 Key descriptive information of midostaurin

Overview of comparator	
Generic name	Midostaurin
ATC code	L01EX10
Mechanism of action	Midostaurin inhibits multiple receptor tyrosine kinases, including *FLT3* and KIT (see Table 53 for more information). Midostaurin inhibits *FLT3* receptor signalling and induces cell cycle arrest and apoptosis in leukaemic cells expressing *FLT3* ITD or TKD mutant receptors or over-expressing *FLT3* wild type receptors.
Method of administration	Oral administration

Overview of comparator	
Dosing	**Induction**: 50 mg orally twice daily at approximately 12-hours intervals on days 8-21. **Consolidation**: 50 mg orally twice daily at approximately 12-hours intervals on days 8-21. **Maintenance**: 50 mg orally twice daily at approximately 12-hours intervals, until relapse for up to 12 cycles of 28 days each. Patients receiving HSCT should discontinue midostaurin 48 hours prior to the conditioning regimen.
Dosing in the health economic model (including relative dose intensity)	Similarly to quizartinib by applying a 95% RDI reported in NICE TA523 (31)
Should the pharmaceutical be administered with other medicines?	**Induction**: Daunorubicin IV (60 mg/m^2 daily on days 1-3) and cytarabine IV (200 mg/m^2 daily on days 1-7). **Consolidation**: four 28-day cycles of high-dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5). **Maintenance**: None.
Treatment duration/criteria for end of treatment	If a diagnosis of infection is made, appropriate treatment must be instituted promptly, including, as needed, the discontinuation of midostaurin. Midostaurin should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease or pneumonitis without an infectious aetiology that are ≥Grade 3 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]). Criteria for end of treatment in the maintenance phase: Relapse or when twelve 28-days cycles have been reached. If neutropenia (absolute neutrophil count [ANC] <1.0 x 10^9/l) persists >2 weeks and is suspected to be related to midostaurin, midostaurin should be discontinued. No criteria for end of treatment specific for the induction or consolidation phase.
Need for diagnostics or other tests (i.e. companion diagnostics)	Before taking midostaurin, AML patients must have confirmation of FLT3 mutation (ITD or TKD) using a validated test.
Package size(s)	Rydapt (midostaurin) 56 x 25 mg capsules (blisters) Rydapt (midostaurin) 112 x 25 mg capsules (blisters)

Sources: ClinicalTrials.gov, 2008 (9); European Medicines Agency, 2017 (43); Medicinpriser.dk, 2024 (44).

3.6 Cost-effectiveness of the comparator(s)

In 2018, the DMC issued a positive recommendation for midostaurin as a standard treatment of patients with *FLT3* AML (45).

As mentioned in section 3.5, SC alone was not considered a relevant comparator as described in the Danish treatment guideline and confirmed by Danish KOL, which mentioned that the vast majority all patients receiving SC will receive midostaurin (29, 32).

3.7 Relevant efficacy outcomes

The relevant outcomes included in this submission includes Q-F trial primary, secondary and exploratory endpoints for quizartinib and placebo, and the respective outcomes for midostaurin from the RATIFY trial.

3.7.1 Definition of efficacy outcomes included in the application

The definition of the relevant efficacy outcomes in Q-F is provided in Table 5. For purposes of comparison, the table also provides definitions from RATIFY for the endpoints OS, CR and CIR which are the endpoints investigated in the MAIC (see section 7).

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection	Endpoint
OS (Q-F)	13 August 2021	Overall survival is defined as the time from randomisation until death from any cause.	Medians time to event were derived from Kaplan-Meier (KM) estimates, CI for medians was computed using the Brookmeyer-Crowley method, HR were derived from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model and confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	Primary
OS (RATIFY)		The period from the date of randomisation until death by any cause. Patients who were alive at the end of study period were censored for this endpoint.		Primary
CR (Q-F)	13 August 2021	CR is defined as neutrophils >1000 cells/mm^3, platelets >100,000 platelets/mm^3 and bone marrow blasts <5%. In Q-F, other requirements include absence of extramedullary disease, absence of blasts with Auer rods, absence of leukemic blasts in the peripheral blood by morphological examination.	Based on Independent Review Committee (IRC) assessment.	Secondary
CR (RATIFY)		CR in RATIFY was assessed by bone marrow examination and defined as an ANC of at least 1,000 per microlitre, a platelet count of at least 100,000 per microlitre, the presence of less than 5% blasts in the marrow or extramedullary leukaemia and the absence of		Secondary

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection	Endpoint
		blasts in the peripheral blood.		
CIR (Q-F)	13 August 2021	CIR from the time of achievement of CR in all subjects who achieved a CR in the induction phase. Relapse after CR was defined as ≥5% blasts in the bone marrow aspirate and/or biopsy not attributable to any other cause; or reappearance of leukemic blasts in the peripheral blood; and/or new appearance of extramedullary leukaemia; or presence of Auer rods	CIR rates were estimated using the cumulative incidence function. Death prior to relapse were considered a competing risk	Exploratory
CIR (RATIFY)		CIR (for patients who have achieved CR after study treatment initiation), is measured from the date of first CR to relapse or death due to AML, whichever occurs first. Relapse after CR was defined as >5% blasts in the marrow, not attributable to another cause (e.g. CSF and bone marrow regeneration), or the reappearance of circulating blast cells not attributable to 'overshoot' following recovery from myelosuppressive therapy or development of extramedullary leukaemia.	CIR rates were estimated using the cumulative incidence function. Death prior to relapse were considered a competing risk	Secondary
EFS (Q-F)	13 August 2021	EFS is time from randomisation to the earliest date of either refractory disease (or treatment failure), relapse, or death from any cause.	The primary analysis of EFS was based on the response assessment by the IRC. For further details, please refer to the row describing OS in this table.	Secondary
RFS (subjects in CR) (Q-F)	13 August 2021	RFS (subjects in CR) is the time from randomisation, for subjects who achieve CR in the induction phase, until the	Please refer to the row describing OS in this table.	Exploratory

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection	Endpoint
		date of documented relapse or death from any cause, whichever comes first.		
RFS (subjects in composite CR [CRc]) (Q-F)	13 August 2021	RFS (subjects in CRc) is the time from randomisation, for subjects who achieve CR or complete remission with incomplete neutrophil or platelet recovery (CRi) in the induction phase, until the date of documented relapse or death from any cause, whichever comes first.	Please refer to the row describing OS in this table.	Exploratory
Duration of CR (Q-F)	13 August 2021	Duration of CR is the time from the first documented CR until the date of documented relapse or death from any cause.	Please refer to the row describing OS in this table.	Exploratory
HSCT rate (Q-F)	13 August 2021	HSCT rate	Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens).	Exploratory
Time to treatment discontinuation (Q-F)	13 August 2021	Time to discontinuation of treatment from any cause	Please refer to the row describing OS in this table.	Post-hoc analysis

Notes: * Time point for data collection used in analysis (follow up time for time-to-event measures).
Source: ClinicalTrials.gov, 2016 (46); ClinicalTrials.gov, 2008 (9); Daiichi Sankyo, Inc., 2022 (8); Daiichi Sankyo, Inc., 2023 (7).

Validity of outcomes

OS was the primary outcome in Q-F and a standard outcome used in oncology studies (10). In the DMC's protocol for the assessment of using midostaurin among patients with *FLT3+* AML, CR, transplantation rate, and EFS were endpoints requested by DMC in the application (47). This supports the inclusion of OS, CR (including durations of CR), transplantation rate, and EFS. RFS, duration of CR, and transplantation rate were exploratory endpoints in Q-F (46).

4. Health economic analysis

A health economic analysis was conducted to estimate the cost effectiveness of quizartinib versus midostaurin for the treatment of de novo FLT3-ITD+ AML patients. In absence of midostaurin efficacy data from Q-F, a MAIC was conducted to estimate the comparative efficacy of quizartinib versus midostaurin for the treatment of de novo FLT3-ITD+ AML

patients. The MAIC is described in detail in section 7 and in Appendix C. Since the comparator trial included a younger population, age adjustment of the intervention data was necessary to ensure a fair comparison and mitigate potential confounding effects. However, the ITT population remains the most relevant for assessing the intervention's real-world applicability, as it reflects the broader, more diverse target population. Thus, while age adjustment was important for comparison with midostaurin, the ITT population provides the most comprehensive evaluation of the intervention's impact and is therefore presented in Appendix B.

4.1 Model structure

The cost-effectiveness analysis was conducted using a semi-Markov model. A schematic illustrating the model structure is outlined in Figure 1.

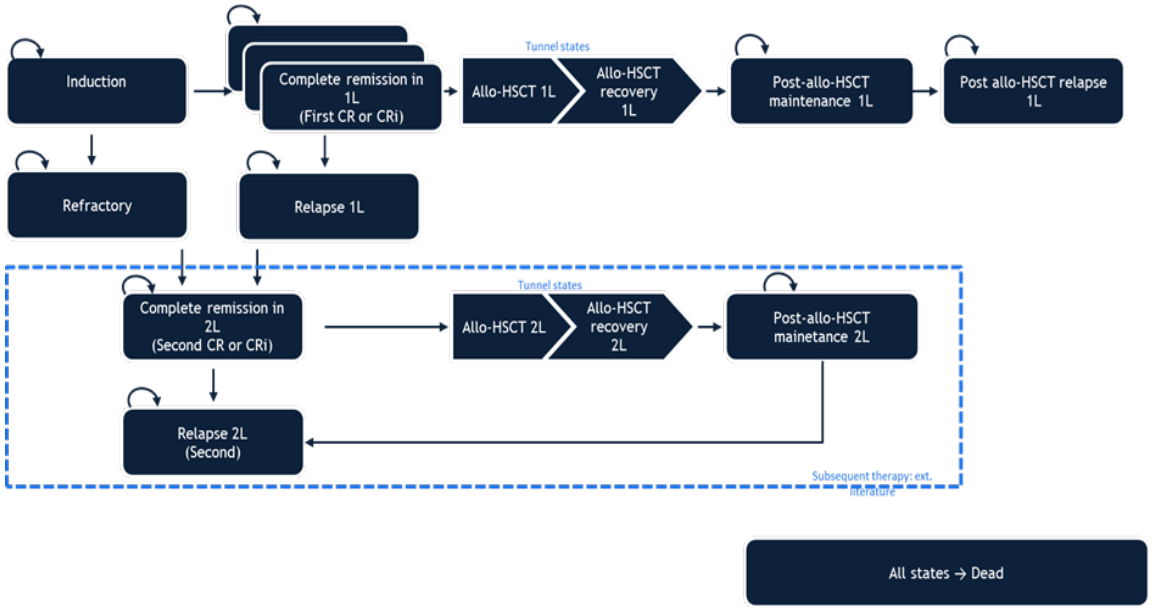


Figure 1. Model schematic

The model states are defined as described in Table 6. The model uses a cycle length of 28 days which is consistent with the length of treatments cycles for quizartinib and midostaurin.

Table 6. Model health states

Health state	Description
Induction	Patients enter the model in the *Induction* health state, where they remain for a maximum of two cycles. Patients can move from *Induction* to the *CR1*, *Refractory* or *Death* health states. In this health state patients receive induction treatment in line with their assigned treatment regimen
CR1	After **induction**, patients who achieve CR or CRi enter the *CR1* health state. On entering *CR1*, patients start **consolidation** treatment for up to four cycles. Those who complete the consolidation treatment will continue to **maintenance** treatment in the *CR1* health state, which lasts up to 36 cycles for the quizartinib strategy, and up to 12 cycles for the midostaurin regimen. Patients remain in the *CR1* state after end of maintenance treatments as long as they do not relapse or receive HCT. Patients are allowed to transition into the *HSCT 1L* health state once they entered the *CR1* (i.e. patients may transition into the *HSCT 1L* health state at any point before

	completion of consolidation and maintenance treatment). Patients can relapse during any phase of *CR1* and so they may not complete the full number of consolidation and maintenance treatment cycles. To capture patient transitions accurately, there are two cohorts of patients entering *CR1*: those who responded after one cycle of induction, and those that responded after two cycles. Therefore, the *CR1* state has been split into two states within the model, so that those who transition after a second round of induction have the correct TPs and costs applied.
HSCT:	Patients can only enter HSCT after complete remission (CRc) either in first or second line, respectively *HSCT 1L* from *CR1* or enter *HSCT 2L* from *CR2*. This consists of a tunnel state of 13 model cycles: • *HSCT*, which lasts 3 model cycles (representing the period while the procedure of transplantation occurs; patients are not receiving quizartinib or comparators during this time) • *HSCT recovery*, which represents the period of recovery after transplant and lasts 10 cycles during which the maintenance treatment can begin. *HSCT* state aligns with the clinical pathway of patients receiving HSCT. Tunnel states were used within the HSCT pathway to facilitate time-dependent variation in costs and utilities for the procedure and the recovery period.
Post HSCT maintenance	Following the transplant tunnel states, patients can enter maintenance treatment in first or second line, respectively. This state represents the period following allo-HSCT during which patients maintain response. Patients will remain in this state until they experience a relapse or die. In these health states patients can receive post HSCT maintenance treatment with quizartinib or sorafenib if in the midostaurin arm (as midostaurin is not indicated for post HSCT maintenance)
HSCT relapse 1L	Patients who relapse post-HSCT 1L are not allowed to undergo another HSCT, but are allowed to receive 2L treatment. 2L treatments in the model include FLAG Ida (a combination of fludarabine, cytarabine, idarubicin, and G-CSF) or gilteritinib. Patients are assumed to remain in the *Post-HSCT relapse* state until they die
Refractory	Patients who fail to achieve *CR1* in response to induction therapy move to the *Refractory* health state. These patients will receive 2L treatment. Those who do not achieve CR or CRi, even those who experience a partial response to treatment, are all assumed equivalent to refractory patients (i.e. patients who do not achieve CR).
Relapse (1L and 2L)	Patients who achieve CR (and thus enter *CR1*) but who then relapse enter the *Relapse1* health state. These patients will receive 2L treatment and if they achieve CR again, transition to *CR2*. Patients who relapse after either entering the *CR2* health state or after having an HSCT in 2L enter the *Relapse2* health state. Patients who enter this state remain here until they die, as 3L treatment is not modelled.
CR2	Patients who did not respond to induction therapy or whose response has waned (e.g. those in the *Refractory* or *Relapse1* states) but respond (CR or CRi) to 2L treatment will enter *CR2*. Patients will remain in the *CR2* state until they receive HSCT, relapse, or die.
Death	patients from all states can die at any time

The model structure was based on economic models from previous HTA submissions for the same indication. A systematic literature review (SLR) was conducted to identify previous economic evaluation for this indication (described in Appendix J). Since CEA was not required during the midostaurin submission in Denmark, most information was drawn from the assessment of midostaurin by NICE(TA523), nevertheless, when possible, outcomes from the midostaurin Danish assessment were used.

The current model structure was developed to address the key limitations identified by NICE reviewers in assessment of Midostaurin (TA523), (8, 9). A comprehensive description for each difference evaluated between the midostaurin NICE submission model and the

one conducted for the assessment of quizartinib in this dossier is included in Appendix K. The key advantages of the current model versus the one used in TA523 are the following:

- 2L treatments are adequately modelled, allowing to estimate patients achieving CR from subsequent treatments.
    - To allow for incorporation of additional relevant health states, a semi Markov structure was deemed appropriate.
- Patients can relapse after HSCT treatment whereas in the midostaurin model all HSCT patients would remain in this state until death; a limitation noted in both the NICE and Danish assessments of midostaurin.
- Refractory patients are modelled separately from patients who relapse.

4.2 Model features

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Patients with newly diagnosed *FLT3-ITD+* AML	In line with this submission indication
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (53 years)	Lifetime, based on mean age at diagnosis in the modelled population (47 years).
Cycle length	28 days	Consistent with length of treatment cycle (day 1 every 28 days)
Half-cycle correction	Yes	-
Discount rate	3.5 % per year	According to DMC methods guide
Intervention	quizartinib	-
Comparator(s)	midostaurin	According to national treatment guideline. Validated by Danish clinical expert
Outcomes	Death after CRc censored by HSCT, Relapse after CRc censored by HSCT, CRc rate at the end of first induction cycle, CRc rates after induction, HSCT rate	Key efficacy outcomes supporting the health economic model structure

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment of quizartinib is based on the head-to-head Q-F trial of quizartinib vs placebo. The clinical assessment of midostaurin is based on the head-to-head RATIFY trial of midostaurin vs placebo. An SLR was conducted, as there is no head-to-head study of quizartinib vs. midostaurin. The literature search is described in Appendix H. In

Table 8, the publications referring to the trials identified in the SLR and from targeted literature review are described.

Table 8 Relevant literature included in the assessment of efficacy and safety.

Reference (Full citation incl. reference number)*	Trial name *	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Daiichi Sankyo, Inc., 2022. A Phase 3, Double-blind, Placebo-controlled Study of Quizartinib Administered in Combination with Induction and Consolidation Chemotherapy, and Administered as Continuation Therapy in Subjects 18 to 75 Years Old with Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (Q-F). (Clinical Study Report: AC220-A-U302.). Data on file (8)[Ω] Erba HP, et al. Q-F Study Group. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (Q-F): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023 May 13;401(10388):1571-1583 (10) Erba, H. et al. AML-029 quizartinib prolonged overall survival (OS) vs placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients aged 18-75 years with newly diagnosed FLT3–internal tandem duplication positive (FLT3-ITD+) acute myeloid leukemia (AML). Clinical Lymphoma Myeloma and Leukemia. 2022, 22, S208-S209 (48). Erba, H. et al. S100: Quizartinib prolonged survival vs placebo plus intensive induction and consolidation therapy followed by single-agent continuation in	Q-F	NCT02668653	Start: 29/01/16 Completion: 13/08/21	Chemotherapy[¥] + quizartinib vs. chemotherapy[¥] + placebo for patients with *FLT3*-ITD+ AML.

Reference (Full citation incl. reference number)*	Trial name *	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
patients aged 18-75 years with newly diagnosed FLT3-ITD+ AML. HemaSphere. 2022, 6, 1-2 (49). Schlenk, R. et al. Quizartinib verlängert das Leben im Vergleich zu Placebo plus intensiver Induktionstherapie und Konsolidierungstherapie gefolgt von einer Behandlung mit Monotherapie bei Patienten im Alter von 18-75 Jahren mit neu diagnostizierter FLT3-ITD und AML [Abstract]. Oncology Research and Treatment. 2022, 67 (50).				
Stone RM, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3;377(5):454-464 (2). Rücker FG, et al. Molecular landscape and prognostic impact of FLT3-ITD insertion site in acute myeloid leukemia: RATIFY study results. Leukemia. 2022 Jan;36(1):90-99. doi: 10.1038/s41375-021-01323-0 (3). Voso, M. T. et al. Midostaurin in patients with acute myeloid leukemia and FLT3-TKD mutations: a subanalysis from the RATIFY trial. Blood Adv. 2020, 4(19), 4945-4954 (51). Dohner, et al. Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. Blood. 2020, 135(5), 371-380 (52). Tzogani, K. et al. . European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis. ESMO Open. 2019, 4(6) (53). Larson, R. A. et al. Midostaurin reduces relapse in FLT3-mutant acute myeloid leukemia: the Alliance CALGB 10603/RATIFY trial. Leukemia. 2021, 35(9), 2539-2551 (54).	RATIFY	NCT00651261	Start: 02/04/08 Completion: July 2016	Chemotherapy¥ + midostaurin vs. chemotherapy¥ + placebo for patients with FLT3 AML.
Matching Adjusted Indirect Treatment Comparison of quizartinib versus midostaurin. Data on file (7) Ω	MAIC of quizartinib		21/02/2024	Chemotherapy¥ + quizartinib vs. chemotherapy¥ + midostaurin for

Reference (Full citation incl. reference number)*	Trial name *	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
	and midostaurin in AML			patients with FLT3-ITD+ AML.

Notes: * If there are several publications connected to a trial, include all publications used. ¥ Chemotherapy was only administered in the induction and consolidation phase. In the maintenance phase, the intervention or the comparator was administered as a single agent. Ω Reference not identified from SLR, as the reference is data on file.

5.2 Literature used for the assessment of health-related quality of life

EQ-5D-5L data was collected as an exploratory endpoint in Q-F but values were not available for all the health states included in the model. An SLR was therefore conducted to identify the most relevant HRQoL study to complement trial data where necessary. The complete literature search is described in Appendix I. Health state utilities collected in Q-F were used for the available health states (*induction, refractory, consolidation, and CR1*) as recommended by the DMC guidelines in the base case, and literature values were applied otherwise. Specifically, values reported in NICE TA 523 were used to inform HRQoL of patients in the HSCT health states. As recommended by the DMC guidelines, when using literature from NICE or other HTA bodies, the original citation must be provided. Therefor Gulke et al. 2012 (55) and Crott et al. 2010 (56) are specified in the Table 9.

Table 9 Relevant literature included for health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility*	Reference to where in the application the data is described/applied
Q-F EQ-5D-5L with Danish tariffs (6) Ω	Induction: [redacted] Consolidation: [redacted] Continuation: [redacted] Refractory: [redacted] Relapse: [redacted]	Section 10.2.3
Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Can-cer (EORTC) Quality of Life Core	HSCTL 1L: 0.613 HSCTL recovery 1L: 0.810 HSCTL maintenance 1L: 0.826	Section 10.2.3

Reference (Full citation incl. reference number)	Health state/Disutility*	Reference to where in the application the data is described/applied
Questionnaire QLQ-C30. Bone Marrow Transplant. 2012;47(4):473-82 (55) Ω Crott et al 2010 Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ. 2010;11(4):427-34 (56) Ω		
NICE TA 523 (31)	As column above HSCTL 1L: 0.613 HSCTL recovery 1L: 0.810 HSCTL maintenance 1L: 0.826	Section 10.2.3 – Note that as mentioned in the text above, NICE TA523 referenced Gulke et al. 2012 (55) and Crott et al. 2010 (56).

Notes: * For the complete description of the utility values included in the model refer to Section 10.2.3, Ω Not identified in the SLR.

5.3 Literature used for inputs for the health economic model

An SLR was conducted to review the available published data regarding modelling techniques relevant to the current indication and to identify the costs and health care resource used associated with the disease. The literature search is described in Appendix J. The table below describes only the inputs included in the model and derived directly from the published literature (i.e. the literature used to derive the data for the MAIC is not described here).

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. New England Journal of Medicine. 2019;381(18):1728-40 (57).	Subsequent treatments efficacy estimates to inform transition probabilities in the Refractory, Relapse 1L and 2L	Systematic literature review	Section 8.3, Table 27
Perl AE, Larson RA, Podoltsev NA, Strickland S, Wang ES, Atallah E, et al. Follow-up of patients with R/R FLT3-mutation–positive AML treated with gilteritinib in the phase 3 ADMIRAL trial. Blood, The Journal of the American Society of Hematology. 2022;139(23):3366-75 (58).	Subsequent treatments efficacy estimates to inform transition probabilities in the Refractory, Relapse 1L and 2L	Targeted literature review	Section 8.3, Table 27
Styczyński J, Tridello G, Koster L, Iacobelli S, van Biezen A, van der Werf S, et al. Death after hematopoietic stem cell transplantation: changes over calendar	Probabilities of death within the HSCT tunnel states	Targeted literature review	Section 8.3, Table 27

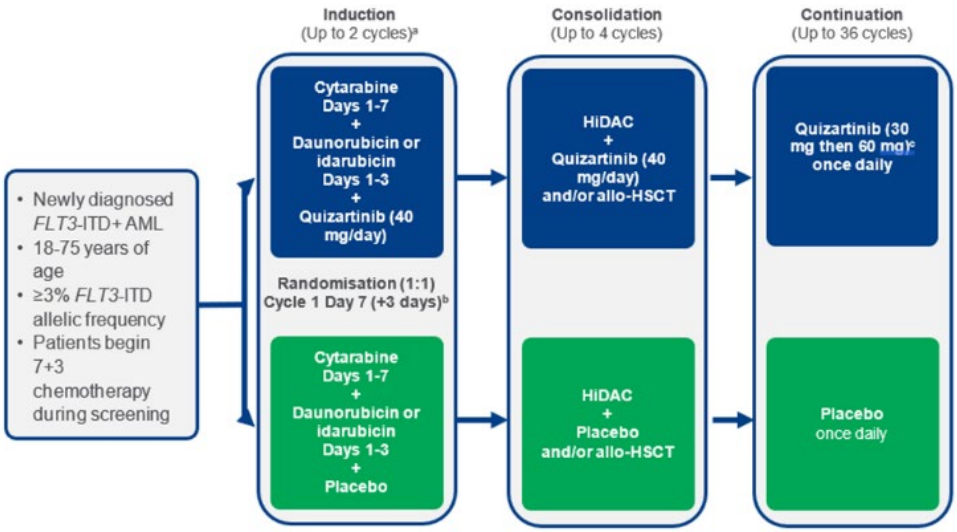
Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
year time, infections, and associated factors. Bone marrow transplantation. 2019;55(1):126-36. (59)			
DMC TA for midostaurin in AML (47)	Resource use	Targeted literature review	Section 11.4 and 11.4.1
Burchert A et al. Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Internal Tandem Duplication Mutation (SORMAIN). J Clin Oncol. 2020 Sep 10;38(26):2993-3002. doi: 10.1200/JCO.19.03345. Epub 2020 Jul 16. PMID: 32673171 (60)	Sorafenib duration of treatment	Targeted literature review	Section 11.1, Table 38

6. Efficacy

6.1 Efficacy of quizartinib compared to midostaurin for patients with *FLT3*-ITD+ AML

6.1.1 Relevant studies

The efficacy and safety of quizartinib versus placebo was investigated in the randomised, double-blind, placebo-controlled, phase III study, Q-F (Figure 2). The study enrolled 539 adult patients between 18 and 75 years of age (25% were 65 years or older), who were newly diagnosed with FLT3-ITD + AML, as determined prospectively by a clinical study assay. Patients were randomised (1:1) to receive quizartinib or placebo for two weeks in each cycle in combination with SC (induction followed by consolidation for responding patients) followed by single-agent maintenance therapy with quizartinib or placebo. The latest data cut-off from the 13 Aug 2021 was used for all endpoints from Q-F . The median follow-up in Q-F was 39.2 months.



Notes: [a] During Cycle 2 of the induction phase, investigators may have chosen to administer the "7 + 3" or the "5 + 2" SC regimen, and study drug would therefore have started on day 8 or day 6, respectively. b Randomisation could be delayed to days 8 to 10 to address clinical concerns.
Source: Erba et al. 2023 (10)

Figure 2. Q-F study design

The efficacy and safety of midostaurin versus placebo plus standard chemotherapy and as single agent maintenance therapy was investigated in 717 patients (18 to 60 years of age) in a randomised, double-blind, phase III study (Figure 3). Patients with newly diagnosed FLT3-mutated AML as determined by a clinical study assay were randomised (1:1) to receive midostaurin or placebo, sequentially in combination with SC induction, consolidation, followed by continuous midostaurin or placebo treatment according to initial assignment for up to 12 additional cycles (9). In RATIFY, the median follow-up time was reported as 59 months for patients who survived.

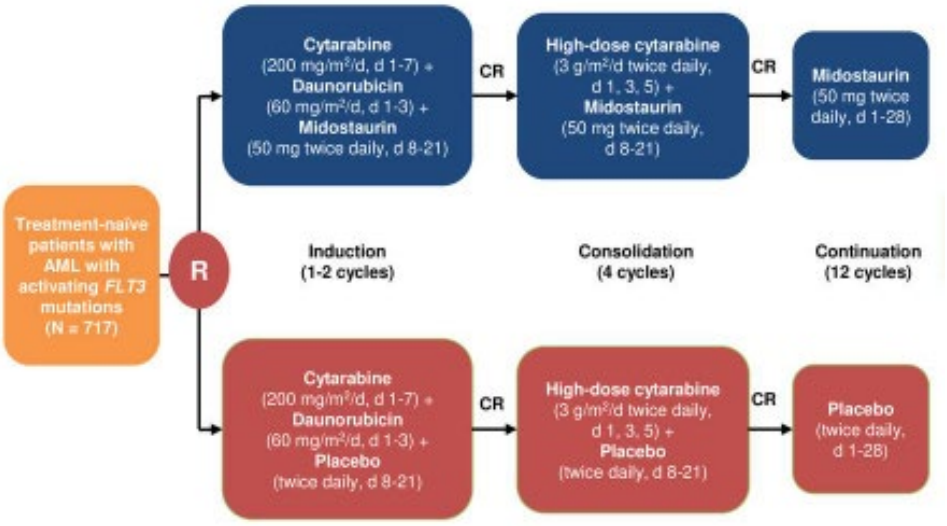


Figure 3. RATIFY study design

An exploratory post-hoc subgroup analysis of RATIFY published by Rücker et al. (2022) including only patients with a *FLT3*-ITD mutation (in alignment with Q-F) was used in the comparative analyses of efficacy (3), and therefore the available results are presented in the following sections.

As requested by DMC on October the 11th 2024, the clinical results for the Q-F subgroup of patients aged <60 years are presented in this section. This focus is because the MAIC analysis informing the comparative efficacy of quizartinib versus midostaurin was conducted on a trimmed Q-F population, to align as closely as possible with the Q-F population to the one of the RATIFY trial. It is noteworthy that, in the Q-F study, age was a prespecified subgroup (<60 years, ≥60 to <65 years, ≥65 years) (8). However, the intent-to-treat (ITT) population remains the most relevant for this indication, in line with the European quizartinib marketing authorisation (1). The clinical results for the ITT population are included in Appendix B and Appendix L.

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Q-F, NCT02668653 Daiichi Sankyo Inc., 2023. Statistical analyses associated to main PAP [data on file] (61). Daiichi Sankyo Inc., 2023. Statistical analyses for AMNOG [data on file] (62). Daiichi Sankyo Inc., 2024. Statistical analyses associated to PAP addendum for Denmark [data on file] (63). Daiichi Sankyo Inc. 2022 Statistical analyses (BDM) [data on file] (64).	Randomised, double-blinded, placebo-controlled, phase III study of quizartinib versus placebo.	Up to 58 months of follow-up.	ITT population Patients 18-75 years of age with newly diagnosed with FLT3-ITD AML.	Induction phase Cycle 1, 28-days: 35.4 mg (2 × 17.7 mg) quizartinib orally once daily on days 8-21 of 7 + 3 (cytarabine [100 or 200 mg/m2/day] IV on days 1 through 8 + daunorubicin [60 mg/m2/day] IV or idarubicin [12 mg/m2/day] IV on days 1-3). Cycle 2, 28-days: 35.4 mg (2 × 17.7 mg) quizartinib orally once daily on days 8-21 or days 6-19 of an optional second induction (7 + 3 or 5 + 2 [5 days cytarabine IV + 2 days daunorubicin IV or idarubicin IV]) Consolidation 35.4 mg (2 × 17.7 mg) quizartinib orally once daily on days 6 to 19 of high-dose cytarabine (1.5-3 g/m2 every 12 hours on days 1, 3, and 5) for up to four 28-day cycles and/or HSCT. Cytarabine among subjects <60 years old: 3.0 g/m2 IV infusion, every 12 hours. Cytarabine among subjects ≥60	Induction phase Cycle 1, 28-days: 35.4 mg (2 × 17.7 mg) placebo orally once daily on days 8-21 of 7 + 3. Cycle 2, 28-days: 35.4 mg (2 × 17.7 mg) placebo orally once daily on days 8-21 or days 6-19 of an optional second induction of 7 + 3 or 5 + 2. Consolidation 35.4 mg (2 × 17.7 mg) placebo orally once daily on days 6 to 19 of high-dose cytarabine (1.5-3 g/m2 every 12 hours on days 1, 3, and 5) for up to four 28-day cycles and/or HSCT. Maintenance Starting dose of 26.5 mg placebo once daily for two weeks if QTcF is ≤ 450 ms. After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg (2 × 26.5 mg) once daily. Single-agent maintenance	OS (approximately 3 years after enrolment), EFS (approximately 3 years after enrolment), CR rate (up to approximately 120 days), composite CR rate (up to approximately 120 days), CR with FLT3-ITD minimal residual disease (MRD) negativity (up to approximately 120 days), composite CR with FLT3-ITD MRD negativity (up to approximately 120 days).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				years old: 1.5 g/m2 IV infusion, every 12 hours. Maintenance Starting dose of 26.5 mg quizartinib once daily for two weeks if QTcF is ≤ 450 ms. After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg (2 × 26.5 mg) once daily. Single-agent maintenance therapy may be continued for up to thirty-six 28-day cycles.	therapy may be continued for up to thirty-six 28-day cycles.	
RATIFY, NCT00651261 Stone RM, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017 Aug 3;377(5):454-464 (2). Rücker FG, et al. Molecular landscape and prognostic impact of FLT3-ITD insertion site in acute myeloid leukemia: RATIFY study results. Leukemia. 2022 Jan;36(1):90-99 (3).	Randomised, double-blinded, placebo-controlled, phase III study of midostaurin versus placebo.	Up to 10 years	Patients < 60 years of age with newly diagnosed FLT3 AML.	Induction 50 mg midostaurin orally twice daily on days 8-21 of daunorubicin 60 mg/m2 IV on days 1-3 and cytarabine 200 mg/m2 IV on days 1-7. Consolidation Patients achieving complete remission received four 28-day cycles of high dose cytarabine (3000 mg/m2) administered over a period of 3 hours every 12 hours on days 1, 3, and 5 and midostaurin 50 mg orally twice daily on days 8-21. Maintenance	Induction 50 mg placebo orally twice daily on days 8-21 of daunorubicin 60 mg/m2 IV on days 1-3 and cytarabine 200 mg/m2 IV on days 1-7. Consolidation Four 28-day cycles of high dose cytarabine (3000 mg/m2) administered over a period of 3 hours every 12 hours on days 1, 3, and 5 and placebo 50 mg orally twice daily on days 8-21. Maintenance Placebo 50 mg orally	OS (up to 10 years), EFS (up to 10 years), OS censoring participants who receive a SCT at the time of the transplant (up to 10 years), CR rate (up to 60 days), disease-free survival (DFS) (up to 10 years), DFS rate one year after completing the planned maintenance phase (30 months).

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				Patients who remained in remission after completion of consolidation therapy entered a maintenance phase in which they received midostaurin 50 mg orally twice daily for twelve 28-day cycles.	twice daily for twelve 28-day cycles.	

Source: ClinicalTrials.gov, 2016 (46); ClinicalTrials.gov, 2008 (9); Daiichi Sankyo, Inc., 2022 (8).

6.1.2 Comparability of studies

Comparisons of trial characteristics revealed heterogeneity between the Q-F and RATIFY populations (7). RATIFY included patients with either *FLT3*-ITD or *FLT3*-TKD mutations, whereas Q-F only included patients with a *FLT3*-ITD mutation. In addition, Q-F enrolled patients aged 18-75, whereas the RATIFY study enrolled patients aged 18-59. However, as stated in section 6.1.1, only the subgroup of patients <60 years of age from Q-F are presented here in section 6. Patients in Q-F could receive either daunorubicin or idarubicin in the induction phase. In RATIFY patients could only receive daunorubicin. While the choice of anthracycline in Q-F was broader, chemotherapy options were considered equivalent between the studies. Patients in Q-F were stratified based on their age, region, and white blood cell (WBC) count, whilst those in RATIFY were stratified by *FLT3* mutation subtype (i.e. *TKD*, *ITD* with low allelic ratio [<0.5] and *ITD* with high allelic ratio [>0.5]) (2), which may have resulted in different distributions of baseline characteristics across the two trials. Treatment with a second induction following residual disease after first induction was composed of '7+3' chemotherapy regimen in RATIFY, while either '7+3' or '5+2' in Q-F. Clinical validation indicated this would not have impacted the efficacy of chemotherapy (7). In terms of outcomes, the definition of OS was consistent across studies and the definitions of CR in Q-F and in RATIFY largely aligned; CR in Q-F was defined as a disappearance of all target lesions after induction while in RATIFY as normalisation of blood counts and a marrow showing less than 5% blasts occurring on or before day 60. The complete

comparison of the outcome definition between the studies and the assumptions taken for the analysis are described in the section 7.1.1.

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients ≤60 years of age from Q-F, the RATIFY ITT population (2), and the RATIFY subpopulation with FLT3-ITD mutation (3) are presented in Table 12. The baseline characteristics for the Q-F overall ITT population, which should be considered as a primary source for assessing the clinical efficacy of quizartinib in line with the EMA indication, are reported in the Appendix B as requested by DMC.

Table 12 Baseline characteristics of patients ≤60 years of age in studies included for the comparative analysis of efficacy and safety (pre matching)

	Q-F (≤60 years of age)		RATIFY (ITT)		RATIFY (*FLT3*-ITD)	
	Quizartinib (N = 161)	Placebo (N = 162)	Midostaurin (N = 360)	Placebo (N = 357)	Midostaurin (N = 230)	Placebo (N = 222)
Median age (range), years	48.0 (23.0-59.0)	48.5 (20.0, 59.0)	47.1 (19.0-59.8)	48.6 (18.0-60.9)	47 (19-59)	48 (18-60)
Sex, female, n (%)	[redacted]	[redacted]	186 (51.7)	212 (59.4)	116 (50.4)	130 (58.6)
Race, n (%)[a]						
White	[redacted]	[redacted]	147/165 (89.1)	128/144 (88.9)	N/A	N/A
Other	[redacted]	[redacted]	18/165 (10.9)	16/144 (11.1)	N/A	N/A
Asian	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Black or African American	[redacted]	[redacted]	N/A	N/A	N/A	N/A
American Indian Or Alaska Native	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Subtype of *FLT3* mutation[b], n (%)						
TKD	[redacted]	[redacted]	81 (22.5)	81 (22.7)	0 (0)	0 (0)
ITD with a low ratio	[redacted]	[redacted]	171 (47.5)	170 (47.6)	80 (34.8)	81 (36.6)
ITD with a high ratio	[redacted]	[redacted]	108 (30.0)	106 (29.7)	149 (65.2)	141 (63.4)
Modified European LeukemiaNet ELN class[c], n (%)						
Favourable	[redacted]	[redacted]	16/269 (5.9)	13/278 (4.7)	34/135 (25.2)	43/133 (32.3)
Normal	[redacted]	[redacted]	172/269 (63.9)	203/278 (73.0)	N/A	N/A
Intermediate II/Intermediate	[redacted]	[redacted]	59/269 (21.9)	45/278 (16.2)	45/135 (33.3)	50/133 (37.6)
Adverse	[redacted]	[redacted]	22/269 (8.2)	17/278 (6.1)	56/135 (41.5)	40/133 (30.1)
Platelet counts (10^3/µL), median (range)	[redacted]	[redacted]	50 (2, 461)	50 (8, 444)	50.5 (2, 461)	49.5 (8, 342)
Cytogenetic risk, n (%)						
Favourable	11 (6.8)	14 (8.6)	N/A	N/A	N/A	N/A
Intermediate	115 (71.4)	114 (70.4)	N/A	N/A	N/A	N/A
Unfavourable	12 (7.5)	17 (10.5)	N/A	N/A	N/A	N/A
Unknown	23 (14.3)	16 (9.9)	N/A	N/A	N/A	N/A

Missing	0	1 (0.6)				
ANC, median (range)	[redacted]	[redacted]	2.2 (0, 55.9) mm^3	2.3 (0, 55.9) mm^3	N/A	N/A
White blood cell count (10^3/µL)						
<40 × 10^9/L	75 (46.6)	77 (47.5)	N/A	N/A	N/A	N/A
≥40 × 10^9/L	86 (53.4)	85 (52.5)				
Median (10^9/L)	[redacted]	[redacted]	35.6 (6, 421.8)	33 (8, 329.8)	42.6 (0.8, 304)	42.1 (0.8, 329.8)
Bone marrow blasts, median (range)	[redacted]	[redacted]	N/A	N/A	77 (3, 100)	80 (6, 100)
Nucleophosmin 1 (NPM1) mutation, n (%)	[redacted]	[redacted]	N/A	N/A	95/190 (50.0)	108/168 (64.3)

Notes: [a] Race in RATIFY was reported by the patients and was not reported for European patients (195 in the midostaurin group, and 213 in the placebo group). [b] Allelic ratio cut-off for FLT3 mutation used for Q-F < 60 is 0.7 and in the RATIFY ITT analysis published by Stone et al, while 0.5 for the analysis published by Rucker et al. (FLT3-ITD+ RATIFY population). [c] Cytogenetic data according to a modified European Leukemia Net classification were available for 547 patients (269 in the midostaurin group, and 278 in the placebo group).
Source: Daiichi Sankyo, 2023, table 1.1.1, table 1.2.1 (61); European Medicines Agency, 2023 (1); Stone et al., 2027 (2); Rücker et al., 2022 (3).

As outlined in Table 12, differences in baseline characteristics of the Q-F and the RATIFY ITT population were observed for allelic ratio, platelet counts, and absolute neutrophil count. Characteristics that could not be assessed for similarity across the studies due to reporting limitations in both trials were patients' race, ELN, cytogenetic risk, white blood cell count, bone marrow blasts, and NPM1. Baseline characteristics provided for the overall ITT population were mostly also provided for the ITD+ population of RATIFY, except for race and ANC. Similarity was visible between the two RATIFY populations regarding patients' age, sex, and platelet count. Baseline characteristics of Q-F <60 years and RATIFY ITD+ population were similar regarding age, sex, and bone marrow blasts, while differences were observed for allelic ratio, platelet count, and NPM1. Differences between trials were addressed by conducting the MAIC (described in section 7).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In Table 13 are presented the characteristics of patients in the Danish population, as suggested by clinical expert, and the one included in the model. The clinical expert suggested that the age of patients in clinical practice should be more closely aligned with the Q-F ITT population. In the economic model, the age reflects the values derived from the Q-F adjusted population through the MAIC, ensuring consistency with the RATIFY trial.

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population FLT3-ITD AML (32)	Value used in health economic model (MAIC adjusted Q-F)
Age in years, mean	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]
Weight, kg	[redacted]	[redacted]
Height, cm	[redacted]	[redacted]

Source: Clinical experts, 2024 (32).

6.1.4 Efficacy – results per QuANTUM First

The median follow-up in Q-F was reported as 39.2 months for both the quizartinib and placebo arms, 95% CI (37.2, 41.5) and (36.3; 41.2), respectively.

As specified in section 6.1.1, this section presents clinical results for the Q-F subgroup of patients aged <60 years old. This focus stems from the MAIC analysis, which compared quizartinib and midostaurin using a trimmed Q-F population to align with the RATIFY trial. Nonetheless, the ITT population remains the most relevant for this indication, consistent with the European marketing authorisation, and it is described in Appendix B and Appendix L.

Discontinuation was similar in both groups (quizartinib: [redacted]%, placebo: [redacted]%). The key reasons included refractory disease ([redacted]%, [redacted]%), relapse ([redacted]%, [redacted]%) and AE ([redacted]% vs. [redacted]%). Other reasons like subject decisions, investigator decisions, and non-protocol therapy were reported at lower rates in both groups (63).

Across the Q-F trial endpoints for the <60 population, if not otherwise specified, median time to events were derived from KM estimates, CI for medians was computed using the Brookmeyer-Crowley method, HR were derived from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model and confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.

6.1.4.1 Overall survival

Treatment with quizartinib resulted in a statistically significant OS benefit compared with placebo (HR 0.684 (0.493, 0.949), p-value [redacted]), corresponding to a 31.6% relative risk reduction of death in favour of the quizartinib arm. The median OS was not reached in the quizartinib arm compared with 23.0 (13.0, NE) months in the placebo arm (Table 14). The OS rate at all time points (from 6 months to 48 months) was higher in the quizartinib arm compared to in the placebo arm.

Table 14 Overall survival (Q-F < 60)

Estimate	Quizartinib (n=161)	Placebo (n=162)
Subjects (%) with events (deaths)	63 (39.1)	83 (51.2)
Median OS months (95% CI)	NE (NE, NE)	23.0 (13, NE)
HR (relative to placebo), 95% CI	0.684 (0.493, 0.949)	
p-value	[redacted]	
6 months OS rate, % (95% CI)	[redacted]	[redacted]
12 months OS rate, % (95% CI)	[redacted]	[redacted]
24 months OS rate, % (95% CI)	[redacted]	[redacted]
36 months OS rate, % (95% CI)	[redacted]	[redacted]
48 months OS rate, % (95% CI)	[redacted]	[redacted]

Source: Daiichi Sankyo Inc., 2024, table 4.4.2a (63).

Figure 4 shows The KM plot of OS. The curves cross at approximately 5 months, probably due to death from infections as observed also in the RATIFY trial, which are a known risk for patients with newly diagnosed AML receiving intensive chemotherapy. After that, there is a clear separation between the quizartinib arm and the placebo arm favouring quizartinib.

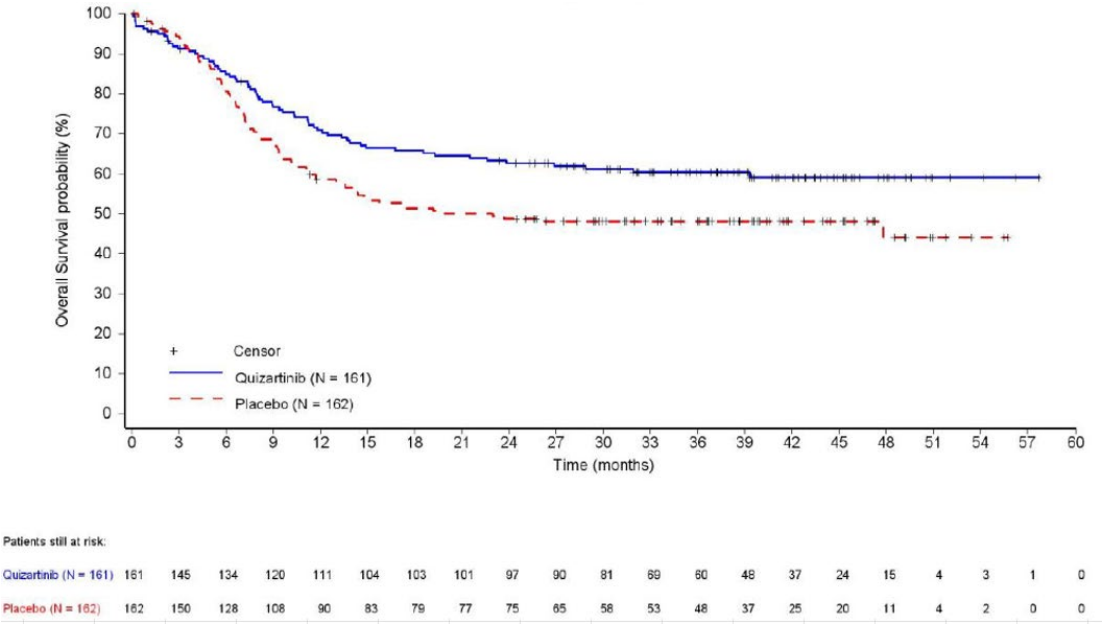


Figure 4 KM plot of overall survival (Q-F < 60)

Source: Daiichi Sankyo Inc., 2024, Figure 4.4.2a (63).

6.1.4.2 Event-free survival

Event-free survival was collected as a secondary endpoint in Q-F. Description of the data is provided in appendix M.1 rather than the main part of the dossier as the health economic analysis do not utilize efficacy data from this endpoint.

6.1.4.2.1 Complete remission endpoints

Table 15 provides an overview of the results of analyses of CR endpoints per IRC assessment. Numerically higher CRc rates were observed in the quizartinib arm ([redacted]%) compared to the placebo arm ([redacted]%) and were driven by higher rates of CRi in the quizartinib arm ([redacted]%) than in the placebo arm ([redacted]%).

Table 15 CR endpoints – (Q-F < 60)

Estimate	Quizartinib (n=161) n (%), (95% CI)	Placebo (n=162) n (%), (95% CI)
CR	90 (55.9), (47.9, 63.7)	90 (55.6), (47.6, 63.4)
Median CR months (95% CI)	[redacted]	[redacted]
HR (relative to placebo), 95% CI	[redacted]	
p-value	[redacted]	
CRi	[redacted]	[redacted]
Median CRi months (95% CI)	[redacted]	[redacted]
HR (relative to placebo), 95% CI	[redacted]	
p-value	[redacted]	
CRc (CR + CRi)	[redacted]	[redacted]
Median CRc months (95% CI)	[redacted]	[redacted]
HR (relative to placebo), 95% CI	[redacted]	
p-value	[redacted]	

Source: Daiichi Sankyo Inc., 2023, table 4.25.2, table 4.24.2 (62); Daiichi Sankyo Inc., 2024, table 4.4.5a, table 4.4.2f (63).

6.1.4.3 Cumulative incidence of relapse

A post-hoc analysis was performed to analyse the CIR in all subjects who achieved a CR in the induction phase treating death prior to relapse as a competing risk (IRC assessment). The CIR rates were numerically lower in the quizartinib arm than the placebo arm, as shown in Table 16. Medians were not reached in either quizartinib or placebo arm.

Table 16. CIR in patients who achieved CR in induction (Q-F < 60)

Estimate	Quizartinib (n=90) n (%)	Placebo (n=90) n (%),
Subjects with event (relapse)	18 (20.0)	31 (34.4)
Subjects with competing risk (death)	8 (8.9)	16 (17.8)
Subjects without events (censored)	64 (71.1)	43 (47.8)

Table 17 CIR rates

CIR rate (%, 95% CIa) at:	Quizartinib (n=161)	Placebo (n=162)
12 months	13.4 ([redacted]	28.4 ([redacted])
24 months	22.6 ([redacted])	37.8 ([redacted])
36 months	22.6 ([redacted])	37.8 ([redacted])

Abbreviations: CI = confidence interval; CIR= cumulative incidence of relapse; CR = Complete remission; IRC = Independent Review Committee; Q-F = Quantum-First.
Notes: [a] Estimated using the cumulative incidence function.
Source: Daiichi Sankyo Inc., 2023, table 14.2.2.5.1 (64).

The CIR curves are shown in Figure 5 indicating a clear separation between the quizartinib arm and the placebo arm favouring quizartinib. Both curves appear to plateau after approximately 24 months.

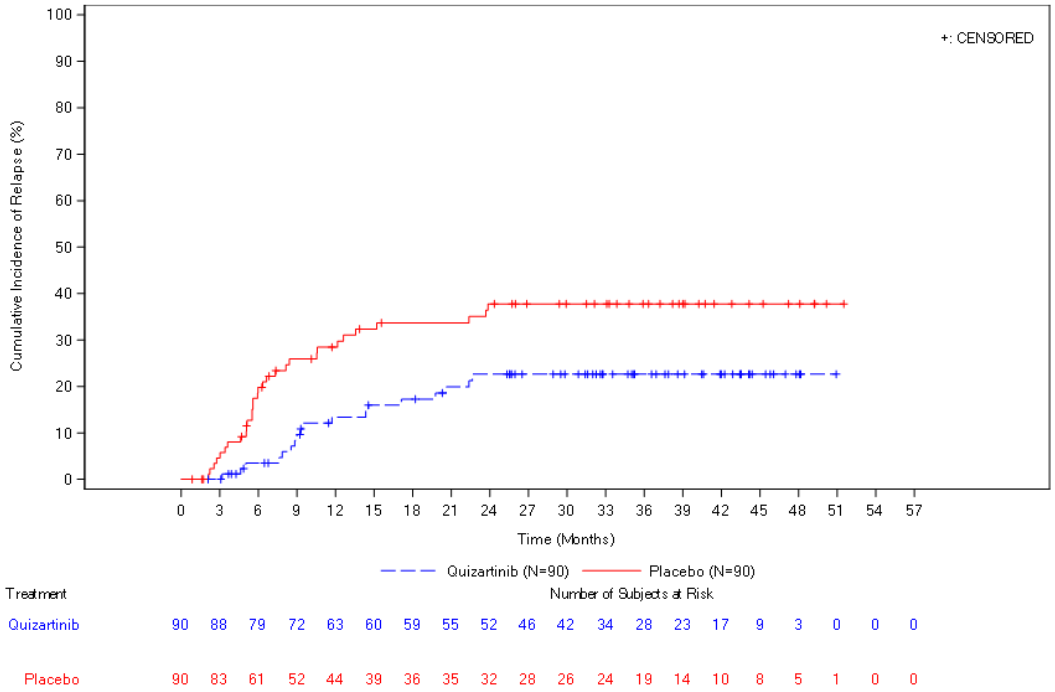


Figure 5. KM plot of CIR for subjects achieving CR in induction (Q-F<60)

Source: Daiichi Sankyo Inc., 2023, figure 14.2.2.5.1 (64).

6.1.4.4 Relapse free survival for subjects achieving CRc in induction

RFS was included in Q-F as an exploratory endpoint. The median RFS in subjects achieving CRc during the induction phase was [redacted] months in the quizartinib arm and [redacted] months in the placebo arm (Table 18).The HR was [redacted]. The corresponding KM plot is presented in Figure 6.

An additional analysis of RFS was completed which defined RFS as for patients who achieved CR (rather than CRc as in the protocol definition of RFS) during induction, until the date of documented relapse or death from any cause, whichever occurred first. The results of this endpoint are described in Table 54 for the <60 population and in Table 55 for the ITT population.

Table 18 RFS for subjects achieving CRc in induction (QF<60)

Statistics	Quizartinib (N=161)	Placebo (N=162)
Subjects with CR	[redacted]	[redacted]
Subjects (%) with events	[redacted]	[redacted]
Subjects (%) censored	[redacted]	[redacted]
Median RFS, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
p value	[redacted]	
RFS rate, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]

Sources: Daiichi Sankyo, 2024, table 4.4.2d (63).

Figure 6 KM of RFS for subjects who achieved CRc in induction (Q-F < 60)

Source: Daiichi Sankyo Inc., 2024, figure 4.4.2d (63).

6.1.4.5 Duration of complete remission

Duration of complete remission was collected as a secondary endpoint in Q-F. Description of the data is provided in appendix M.2 rather than the main part of the dossier as the health economic analysis do not utilize efficacy data from this endpoint.

6.1.4.5.1 Transplantation rate

Transplantation rate was included in Q-F as an exploratory endpoint. A total of [redacted] ([redacted]%) subjects in the quizartinib arm and [redacted] ([redacted]%) subjects in the placebo arm underwent an HSCT. Of these, [redacted] ([redacted]%) and 64 ([redacted]%) of subjects received protocol specified HSCT in the quizartinib and placebo arms respectively (Table 19).

Table 19. HSCT rate (Q-F < 60)

	Quizartinib (N=161)	Placebo (N=162)
Protocol-specified HSCT[a], n (%) [95% CI][b]	[redacted]	[redacted]
Non-protocol-specified HSCT, n (%)	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HSCT = haematopoietic stem cell transplantation; Q-F=Quantum-First.
Notes: [a] Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens).
Sourcess: Daiichi Sankyo, 2024, table 4.4.3a (63).

6.1.4.6 Time to discontinuation

Time to discontinuation is an additional endpoint included in Q-F. Median time to treatment discontinuation was [redacted] months ([redacted], [redacted]) for quizartinib and [redacted] months ([redacted], [redacted]) for placebo. The HR was [redacted] ([redacted], [redacted]).

Figure 7. KM plot for time to discontinuation (Q-F <60)

Sourcess: Daiichi Sankyo, 2023, figure 3.4.2 (61).

6.1.5 Efficacy – results per RATIFY

Detailed information on discontinuation in each study arm is not reported in Stone et al., 2017 (2). However, in 38 patients trial treatment was discontinued immediately after a complete remission was achieved due to: receipt of alternative therapy (11 patients), early disease progression (6), an adverse event (10), patient withdrawal from the trial (8), and other (3). Of the 38 patients, 29 underwent transplantation, including 11 patients who received alternative therapy (2).

6.1.5.1 Overall survival endpoints

In Table 20, the results of the OS endpoints are presented. Median OS was 74.7 months (95% CI 31.5, NE) in the midostaurin group compared to 25.6 months (95% CI 18.6, 42.9) in the placebo group (*P* = 0.009).

Table 20 Summary of OS endpoints (ITT population)

Estimate	Midostaurin (N = 360)	Placebo (N = 357)	Analysis (midostaurin vs. placebo)
Median OS months (95% CI)	74.7 (31.5, NE)	25.6 (18.6, 42.9)	*P* = 0.009*
HR (95% CI)	N/A	N/A	0.78 (0.63, 0.96)
4-year OS rate, %	51.4	44.3	N/A

Notes: * one-sided P-value by stratified log-rank test.
Source: Stone et al., 2017 (2).

Figure 8 shows KM curves for OS. Similarly to what observed in Q-F, the KM curve cross at the beginning of the follow-up due to more infections in the midostaurin arm.

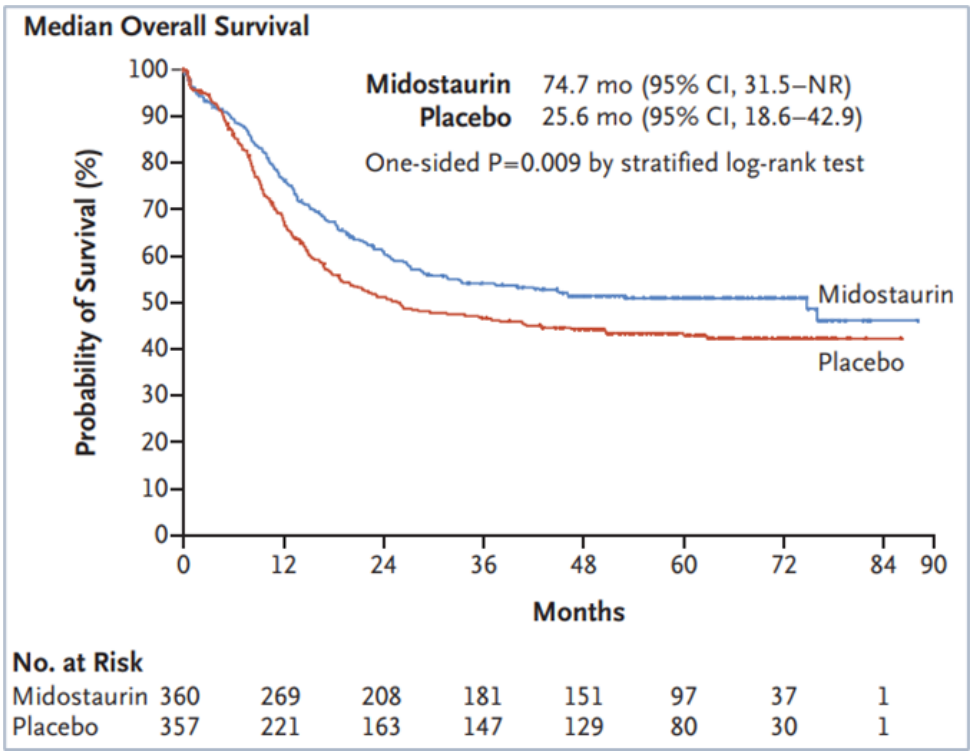


Figure 8. KM plot of overall survival (RATIFY ITT population)

Source: Stone et al. 2017 (2).

Analyses of subgroups according to *FLT3* subtype showed that midostaurin had some benefit, but OS did not differ significantly according to trial regimen within each subgroup (Figure 9).

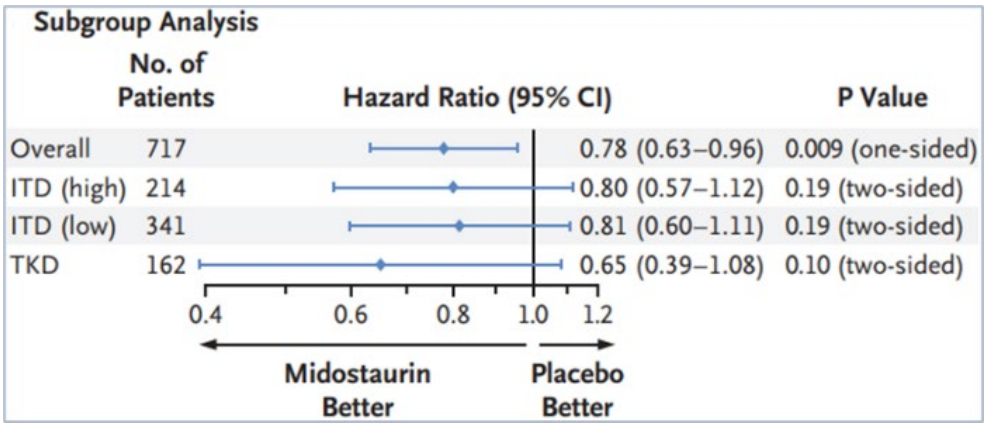


Figure 9. Between-group comparison of overall survival with stratification according to subtype of FLT3 mutation (ITT population)

Notes: Shows the between-group comparison of OS with stratification according to subtype of FLT3 mutation: point mutation in the TKD or ITD mutation with either a high ratio (>0.7) or a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITD [high] and ITD [low], respectively).
Source: Stone et al. 2017 (2).

6.1.5.2 Event-free survival

Event-free survival was collected as a secondary endpoint in Q-F. Description of the data is provided in appendix M.3 rather than the main part of the dossier as the health economic analysis do not utilize efficacy data from this endpoint

6.1.5.3 Complete remission endpoints

The rate of CR was 58.9% (95% CI 53.6, 64.0) in the midostaurin group and 53.5% (95% CI 48.2, 58.8) in the placebo group (*P* = 0.15) (Table 21).

Table 21. Summary of CR endpoints (ITT population)

Variable	Midostaurin (N = 360)	Placebo (N = 357)	*P*-value†
Protocol-specified CR – n (%), (95% CI)	212 (58.9%) (53.6-64.0)	191 (53.5%), (48.2-58.8)	0.15
Time to CR* in days – median (range)	35 (20-60)	35 (20-60)	

Notes: † *P* value is two-sided and was calculated with the use of Fisher's exact test. * Based on Kaplan-Meier estimate.
Source: Stone et al., 2017 (2).

6.1.5.4 Cumulative incidence of relapse

In RATIFY, a competing risks analysis with death from any cause as a competing risk, was used to compute the cumulative incidence curves for relapse among patients achieving a CR and compared between the arms. A competing risk analysis was conducted as death prevents the occurrence of relapse, which in this case is the primary event of interest. Median CIR was not estimable for both midostaurin and placebo. Similarly to Q-F, both midostaurin and placebo curve appear to plateau at approximately after 24 months.

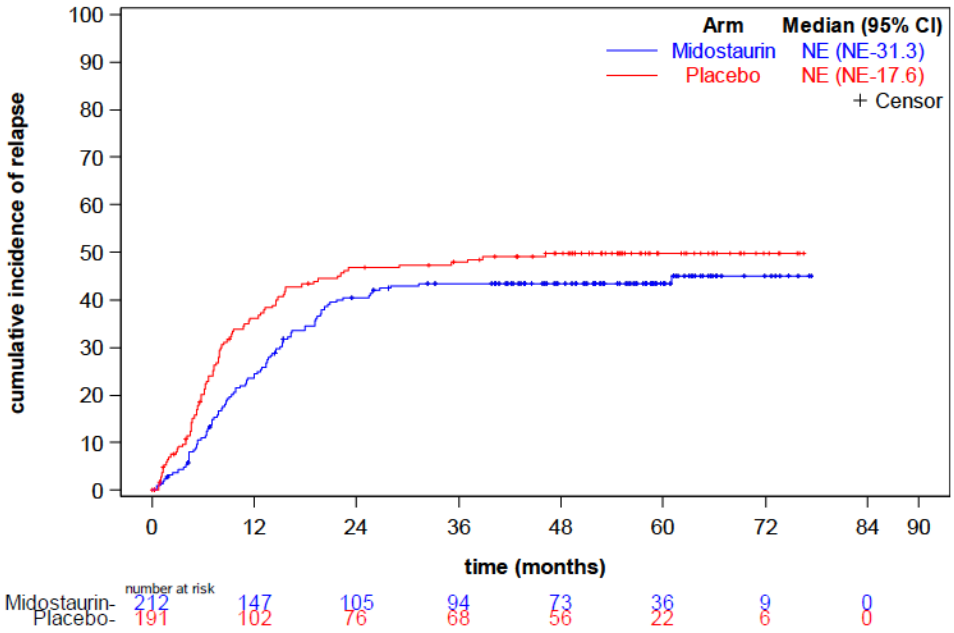


Figure 10. KM plot of CIR treating death as a competing risk (protocol CRs only) in RATIFY

Notes: two sided log-rank p=0.13
Source: Stone et al., 2017. Figure S2B (2).

Cumulative incidence of relapse was investigated in Rücker et al. 2022 (3) and is presented in Figure 11. In the analysis by Rücker et al. 2022, patients were analysed according to their ITD insertion site and classified as insertion site in: the juxtamembrane domain (JMDsole), the tyrosine kinase domain-1 (TKD1sole), or the juxtamembrane domain and tyrosine kinase domain-1 (JMD/TKD1). The 4-year rates for patients on midostaurin vs placebo were 40% vs 50% (P = 0.246) for JMDsole, 56% vs 63% (P = 0.535) for JMD/ TKD1, and 56% vs 63% (P = 0.997) for TKD1sole subgroups, respectively.

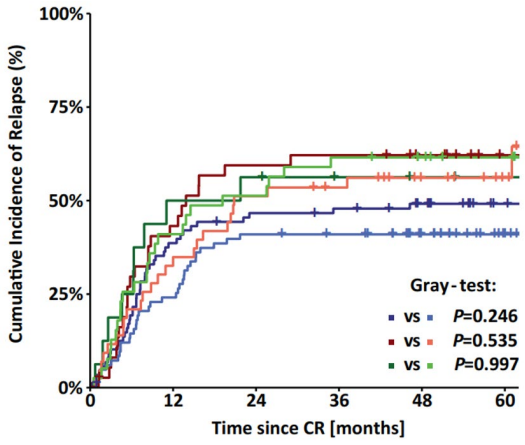


Figure 11 KM plot of CIR (FLT3-ITD population) in RATIFY

Source: Rücker et al. 2022, Figure 4b (3).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

The MAIC compared OS, CR, and CIR outcomes between Q-F and RATIFY. It was not feasible to compare RFS as the definition of the endpoint differed between the two trials. In Q-F the date from randomisation was used as the start date for RFS whilst the equivalent outcome in RATIFY (DFS) used the date at which CR was achieved as the start date of analysis (7). The definition of OS was consistent across both trials. The definitions of CR were largely aligned across the trials; Q-F counted any CR achieved within the two induction cycles patients underwent, encompassing a period up to 120 days. Similarly, RATIFY counted CR until day 60 from randomisation, but allowed a second induction cycle and attributed any CR to the initial 60 days, effectively also considering any CR within 120 days. The definition of CIR was not clearly described in RATIFY introducing some uncertainty. Assuming CIR is defined as the proportion of patients experiencing relapse after achieving CR, the relative components of this definition (i.e. CR and relapse) were similarly defined between the trials. However, the definitions of relapse after CR, which impacts CIR, differed slightly with the 'presence of Auer rods' also indicating relapse in Q-F but not in RATIFY (7).

7.1.2 Method of synthesis

A MAIC was conducted to estimate the comparative efficacy of quizartinib vs midostaurin. Standard methods for indirect comparison and network meta-analysis were not deemed appropriate, as these assumes no difference between trials in the distribution of effect-modifying variables, while the Q-F and the RATIFY study presented a few key differences: First Q-F only included patients with a FLT3 ITD mutation, whereas RATIFY included patients with either FLT3-ITD or FLT3-TKD mutations. Secondly, Q-F included patients between 18-75 years of age, while RATIFY between 18-59.

The MAIC used IPD from Q-F to match baseline summary statistics reported from RATIFY, using covariates measured in the trial with IPD that interact with treatment effect (described in detail in section 7.1.2.2). The covariates are then used to reweight the observations in the IPD from Q-F using propensity score weighting, to match the covariate distribution in RATIFY, where only aggregate data is available. The MAIC therefore provides an estimate of the trial's outcomes (OS, CR and CIR) that would have been observed for patients in the RATIFY trial if they received quizartinib.

7.1.2.1 Feasibility assessment

A feasibility assessment was conducted to assess what type of ITC methodology was appropriate. First, the study design, study conduct, inclusion and exclusion criteria, as well as baseline patients' characteristics of Q-F and RATIFY were compared. This aimed to identify any heterogeneity that would justify using a population-adjusted ITC and to ensure that patient characteristics were defined consistently enough across trials for accurate

population matching. Based on the network diagram (Figure 12) of the treatments in each of the trials, an anchored ITC, with placebo + standard induction and consolidation chemotherapy as the anchor, was considered suitable to analyse the relative efficacy of quizartinib vs. midostaurin.

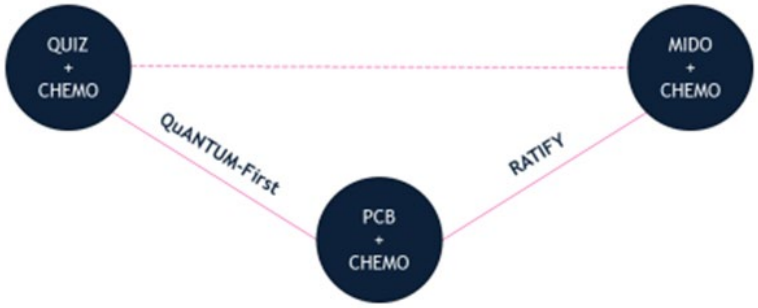


Figure 12. Network of evidence for the indirect comparison of quizartinib and midostaurin

Differences in the inclusion criteria revealed heterogeneity between Q-F and RATIFY. Overall, RATIFY included patients with either TKD or ITD mutations, while Q-F only included FLT3-ITD (+) patients. The RATIFY data were split into ITT and ITD-focused analyses using Stone et al. (2017) and Rücker et al. (2022). Q-F's patient group was older (ages 18-75) compared to RATIFY's (18-59). The trials also had different randomisation factors: RATIFY randomised by FLT3 mutation subtype, while Q-F used age, region, and white blood cell count. Lastly, RATIFY had a longer median follow-up time.

The evaluation of patients' characteristics (described in section 6.1.2.1) revealed that compared to RATIFY, the Q-F patients' population had higher age, lower mean platelet count, lower mean ANC and lower proportion of white patients. Uncertainty surrounded ECOG performance status, patient's demographic region, WBC, karyotypes, and patient's NPM1 mutation status as potential differences could not be assessed for these variables due to reporting limitations in either of the trials.

Heterogeneity between the Q-F and RATIFY arms was noted due to differences in induction chemotherapy options. Q-F allowed patients to choose daunorubicin or idarubicin and offered 7 + 3 or 5 + 2 regimens for a second cycle if needed, while RATIFY patients received only daunorubicin and were limited to the 7 + 3 regimen. However, clinical experts believed these differences were unlikely to bias the relative treatment effects.

7.1.2.2 Determination of the effect modifiers

Effect modifiers were identified through literature review, empirical assessment of Q-F data and expert consultation.

The RATIFY publications were evaluated for clinical subgroup reporting to identify treatment effect modifiers (TEMs). Subgroup analyses included sex, age, FLT3 subtype, ELN risk, NPM1 mutation, and WBC. Among these, only age, NPM1 mutation, and ELN were statistically identified as potential TEMs. Other variables showed no significant results and were excluded.

IPD from Q-F was used to conduct interaction analysis for assessing treatment modifying effects of baseline characteristics. Univariate regression analysis identified FLT3-ITDlow vs. FLT3-ITDhigh status, cytogenetic risk, and bone marrow blasts as treatment effect modifiers for quizartinib combined with chemotherapy on OS. Greater benefit was observed in

patients with FLT3-ITDhigh, intermediate, adverse, or unknown cytogenetic risk, and those with higher bone marrow blasts. Detailed results of the interaction analysis are provided in Table 57.

Clinical expert consultation (7) highlighted age, gender, FLT3 mutation status, platelet count and ANC were TEMs for the outcomes of interest. Race and bone marrow blast were considered as well but scored low on the importance scale. Cytogenetic risk, WBC patient's geographical region, and NPM1 mutation were flagged as potential TEMs as well, with the former two considered most impactful. However, due to unavailability of data across the RATIFY main publication and Q-F, these variables could not be matched on for the comparison of Q-F with RATIFY's ITT population.

Specifically, for the ITD population **age**, **gender**, **FLT3 mutation status**, **platelet count** and **NPM1 mutation** were accounted for as TEM. See the complete overview of TEM variables by derivation technique and inclusion in Table 58.

7.1.2.3 Statistical methods

To allow for a better alignment between the trial populations and improve the robustness of the results avoiding possible extreme weights (65), only IPD of patients aged ≤ 60 years from the Q-F population was used in this analysis (13 Aug 2021 data cut off). Similarly, a subgroup analysis of RATIFY published by Rücker et al. (2022) which included only patients with a *FLT3*-ITD mutation (63.04% of the ITT population) (3), was used in the analysis. Published summary statistics for OS (HR), CR (OR) and CIR (HR) were retrieved from the Rücker et al. publication on ITD (+) patients in the RATIFY trial, and directly used for the MAIC. Propensity score weights were calculated using logistic regression (see Appendix C for complete description of the propensity score weights calculations). Matching variables for the MAIC were included stepwise, starting with the highest-ranking TEM and adding others based on rank, until the ESS with all variables did not drop below 50% of the original sample size. Population overlap was diagnosed by rescaling weights, presented in a histogram in Figure 13 (see Appendix C for the formula used to rescale weights).

To compare quizartinib and midostaurin for OS, CR, and CIR, log hazard ratios (HRs) and odds ratios (ORs) were used as linear predictors as recommended in the NICE MAIC guidelines (65) (see Appendix C for description of treatment effect calculations).

Both unadjusted and adjusted (weighted) estimates of the treatment effects were calculated, with weights applied to make the comparison groups more balanced. To get accurate estimates of the standard errors and confidence intervals for these effects, the researchers used robust sandwich variance estimation and applied bootstrap resampling. In bootstrap resampling, the analysis is repeated 1,000 times with different random samples, to estimate the 95% CI.

7.1.3 Results from the comparative analysis

7.1.3.1 Matched population and propensity score weights

The baseline characteristics before and after matching for Q-F and RATIFY are provided in Table 22. Two of the baseline characteristics identified as TEM (age and sex) were similar across the unadjusted studies. However, platelet counts at baseline, NPM1 mutation status and FLT3 ITD allelic ratio were found to be imbalanced. Platelet count and NPM1 mutations status were used as TEMs for matching while FLT3 ITD allelic ratio could not be matched as the ESS fell below 50% of actual sample size upon inclusion. The Q-F

population ≤ 60 was matched for platelet count, sex, age, and NPM1 mutation status, resulting in an ESS of [redacted], representing a reduction of the sample size by [redacted]

The matched Q-F population showed improved alignment of baseline characteristics with RATIFY for platelet count, sex, age, and NPM1 mutation status. Mean platelet counts after matching aligned closely, but when comparing median platelet counts, a difference remained highlighting it is not certain that all differences in platelet count were resolved.

Table 22. Summary of patient characteristics in the MAIC Q-F≤ 60 and RATIFY *FLT3-ITD*+ population

	QF unadjusted (N = [redacted])	QF adjusted (ESS = [redacted])	RATIFY ITD+ population (N = 452)
TEMs (base case)			
Platelet counts (10^3/µL), mean	[redacted]	[redacted]	50.0[b]
Platelet counts (10^3/µL), median (range)	[redacted]	[redacted]	50 (2, 461)
Sex, female, n (%)	[redacted]	[redacted]	246 (54.4)
Mean age, years	[redacted]	[redacted]	47[a]
Median age (range), years	[redacted]	[redacted]	47 (18-60)
Nucleophosmin 1 (NPM1) mutation, n (%)	[redacted]	[redacted]	203/358 (56.7)
TEMs excluded due to the resulting ESS falling below 50% of the original sample size			
FLT3 ITD with a high ratio (> 0.5)[d]	[redacted]	[redacted]	290 (64.3)
Other variables			
Race, n (%)[c]			
White	[redacted]	[redacted]	N/A
Other	[redacted]	[redacted]	N/A
Asian	[redacted]	[redacted]	N/A
Black or African American	[redacted]	[redacted]	N/A
American Indian Or Alaska Native	[redacted]	[redacted]	N/A
Subtype of *FLT3* mutation[d], n (%)			
TKD	[redacted]	[redacted]	0 (0)
ITD with a low ratio (≤ 0.5)	[redacted]	[redacted]	161 (35.7)
Modified European LeukemiaNet ELN classe, n (%)[e]			

Favourable	N/A	N/A	77/268 (28.7)
Normal	N/A	N/A	N/A
Intermediate II/Intermediate	N/A	N/A	95/268 (35.4)
Adverse	N/A	N/A	96/268 (35.8)
Cytogenetic risk, n (%)			
Favourable	[redacted]	[redacted]	N/A
Intermediate	[redacted]	[redacted]	N/A
Unfavourable	[redacted]	[redacted]	N/A
Unknown	[redacted]	[redacted]	N/A
Missing	[redacted]	[redacted]	
ANC, median (range)	[redacted]	[redacted]	N/A
White blood cell count (10^3/µL)			
<40 × 10^9/L	[redacted]	[redacted]	N/A
≥40 × 10^9/L	[redacted]	[redacted]	
Median (10^9/L)	[redacted]	[redacted]	42.4 (0.8, 329.8)
Bone marrow blasts, median (range)	[redacted]	[redacted]	79 (3, 100)

Notes: a While Q-F was randomised for < and ≥ 60 the Q-F population used in the MAIC was defined as ≤ 60 years old to match as close as possible the RATIFY trial. [b] Given only the median platelet count, the median age and median bone marrow blast count were available from *FLT3*-ITD+ patient population of RATIFY but the matching approach utilises the mean, it was assumed that median and mean were equal. Re-weighting was conducted on the assumed means, but the medians are presented here for comparison.
c: Race in RATIFY was reported by the patients and was not reported for European patients (195 in the midostaurin group, and 213 in the placebo group). d: Allelic ratio cut-off for FLT3 mutation used for Q-F < 60 is 0.7 and in the RATIFY ITT analysis published by Stone et al, while 0.5 for the analysis published by Rucker et al. (FLT3-ITD+ RATIFY population). e: Cytogenetic data according to a modified European Leukemia Net classification were available for 547 patients (269 in the midostaurin group, and 278 in the placebo group).
Reference: Rücker et al., 2022 (3), Daiichi Sankyo, 2023 (7).Reference: Rücker et al., 2022 (3), Daiichi Sankyo, 2023 (7).

Most of the distribution of the resulting weights were centred around one (Figure 13). Four outliers with weights above five were identified in the matching between Q-F and RATIFY, with a maximum weight of [redacted] Investigation of patients with high weights indicated that high weights correlated with high platelet counts. Given the higher median and maximum platelet count in RATIFY, patients with high platelet counts were underrepresented in the Q-F trial population below 60 and received higher weights during matching.

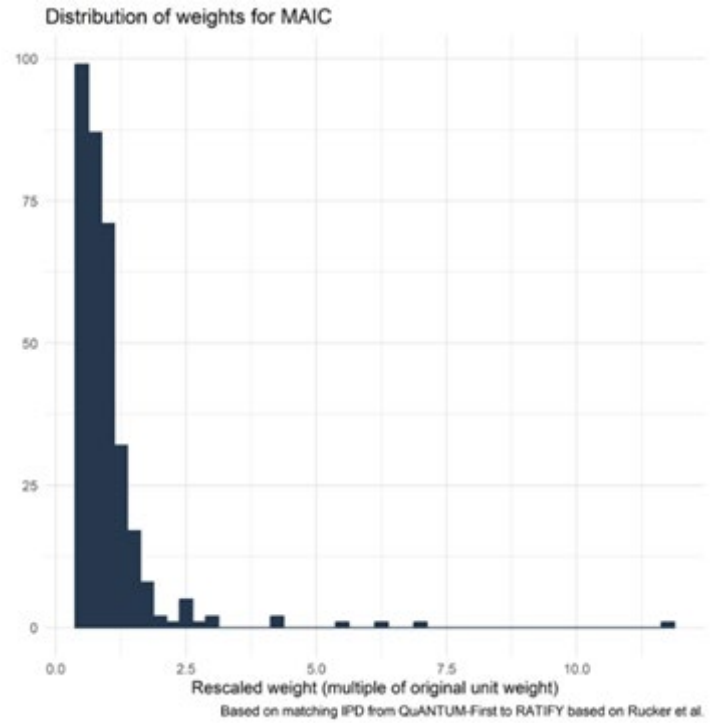


Figure 13. Propensity score weights for Q-F

Source: Daiichi Sankyo, 2023 (7).

Table 23 presents the key results of the comparative analysis of quizartinib vs. midostaurin for the Q-F ≤ 60 and the RATIFY *FLT3*-ITD+ population.

Table 23 Results from the comparative analysis (MAIC) of quizartinib vs. midostaurin for FLT3-ITD+ AML patients

Outcome measure	quizartinib	midostaurin	Result (Difference)
OS (median, months)	Median: NR (95 % CI: NR; NR)	Median: 29.20 months (95 % CI: 24.40; NR)	Difference in medians NE **HR: 0.82 (95 % CI: 0.48;1.39)**
CR (Rate)	58.28% (51.24% - 65.73%)	71.74% (65.92% - 77.56%)	Difference -13.46% (-22.76% - -4.16%) **OR: 0.92 (95 % CI: 0.42;1.97)**
CIR (median, months)	Median: NR (95 % CI: NR; NR)	Median: 37.13 months (95 % CI: 19.67; NR)	Difference in medians NE **HR: 0.42 (95 % CI: 0.20;0.91)**

Source: Daiichi Sankyo, 2023 (7) (MAIC analysis). Data for the quizartinib arm is based on data from Q-F whereas data for midostaurin is based on Rucker et al (3) (see section7.1.2.3)

7.1.4 Efficacy – results per OS

The complete results for OS are reported in Appendix C Prior to matching, both quizartinib and midostaurin demonstrated favourable efficacy versus placebo. Matching shifted upwards the quizartinib and placebo OS curves of Q-F (Figure 21). The median OS before matching in Q-F was not reached for the quizartinib arm and was [redacted] months ([redacted]) for the placebo arm. Post matching, median OS for quizartinib was not reached while the placebo arm had an OS median of [redacted] months ([redacted]). The MAIC results for OS

(showed numerically favourable but not significant outcomes with quizartinib as compared to midostaurin (HR = 0.82 [0.48,1.39]). A naïve comparison indicated a HR of 0.87 between quizartinib and midostaurin.

7.1.5 Efficacy – results per CR

The complete results for CR are reported in Appendix C. Prior to matching, both quizartinib and midostaurin demonstrated favourable efficacy versus placebo, as measured by CR ORs. The MAIC results for CR showed numerically less favourable outcomes but statistically not significant outcomes with quizartinib as compared to midostaurin (OR= 0.92 [0.42,1.97]). A naïve comparison indicated an OR of 0.83 between quizartinib and midostaurin.

The slightly higher CR rates observed for quizartinib could potentially be a result of CR being achieved faster in a healthier population, such as RATIFY compared to the Q-F population, with the MAIC only adequately adjusting for population differences available (see section 6.1.2.1). While not utilized in the health economic analysis a retrospective study across US treatment centers found CRc rates to be higher when treating with quizartinib rather than midostaurin While not utilized in the health economic analysis a retrospective study across US treatment centers found CRc rates to be higher when treating with quizartinib rather than midostaurin ((66), Link: Paper: Real-World Treatment Patterns and Effectiveness of Midostaurin Versus Quizartinib in FLT3-ITD Mutated Acute Myeloid Leukemia Undergoing Intensive Induction)

7.1.6 Efficacy – results per CIR

The complete results for CIR are reported in Appendix C Prior to matching, both quizartinib and midostaurin demonstrated favorable efficacy versus placebo, as measured by the CIR HR. Matching shifted the CIR quizartinib curve downwards, and the placebo curve in Q-F upwards, improving the relative effectiveness of quizartinib versus placebo after matching. The upwards shift of the placebo curve featured two identifiable moments of relapse (around three months and six months) which was caused by placebo patients with a higher weight experiencing relapse events. Using the competing risk approach, the CIR HR of quizartinib versus placebo was favorable significant before and after matching (0.49 and 0.34 respectively). The MAIC results for CIR HR favours quizartinib with significant HR of 0.42 (0.20, 0.91). A naïve comparison indicated a HR of 0.61 between quizartinib and midostaurin.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Transition probabilities (TP) are based on data from Q-F, the MAIC described in section 7, along with a set of additional external data sources. Unless otherwise specified, the MAIC adjusted <60 population from Q-F have been used. Most transitions in the model are informed by time-constant TPs, however time-varying TPs have been used by extrapolation

of time-to event transitions from *CR1* to *Relapse 1* and *Death*. Section 8.1.1 describes methods and assumptions regarding the time-varying TPs whereas 8.1.2 describes assumptions concerning time-constant TPs.

8.1.1 Extrapolation of efficacy data (time-varying transition probabilities)

RFS for subjects achieving CRC in induction censored at the start date of HSCT from the MAIC-adjusted Q-F data was used to estimate transition from *CR1* to *Relapse 1* in the quizartinib arm. Similarly, Death after achieving CRc (censored for HSCT and relapse) was used to inform transition from *CR1* to *Death*. Transitions for the midostaurin arm were estimated by applying the estimated HRs from the MAIC to the extrapolated time to event data for quizartinib (see section 7 and Table 24).

The "flexsurv" package in R was used to fit the seven standard parametric models, exponential, gamma, generalized gamma, Gompertz, log-logistic, log-normal and Weibull as described in NICE DSU TSD 14, to the trial data (67). The complete methodological description of extrapolation methods can be found in Appendix D. The base case curves applied in the model are described in the following paragraphs. See also appendix N.6 for description of the mathematical derivation used to calculate time-varying TPs based on the extrapolated efficacy data.

8.1.1.1 Extrapolation of RFS after CRc (*CR1* to *Relapse1*)

For quizartinib, the independent log-normal distribution was selected to obtain RFS after CRc curves used in the base case analysis (see section 6.1.4.4). In addition, a cure point was implemented at year 3. With the cure approach, patients who remain in *CR1* and *Post-HSCT maintenance 1L* beyond 3 years are assumed to be functionally cured. Three years was selected as the cure point as this is was in line with prior NICE assessments in the AML area for midostaurin and gilteritinib (31, 68). The resulting curves from the extrapolation and cure-point assumption are shown in Figure 14. As described in section 7.1.1, definition of RFS differed in Q-F and RATIFY. Consequently, for midostaurin the HR established for CIR in the MAIC are used as a proxy for RFS to estimate the RFS after CRc curve.

Table 24 Summary of assumptions associated with extrapolation of RFS (MAIC adjusted)

Method/approach	Description/assumption
Data input	Quizartinib: Relapse after CRc censored for HSCT and death from the weighted Q-F population ≤ 60 years matched to the RATIFY FLT3-ITD+ population Midostaurin: MAIC CIR HR 0.42 (95% CI: 0,20;0,91) applied to the quizartinib curve
Model	Full parametrisation
Assumption of proportional hazards between intervention and comparator	Proportional hazard assumption between quizartinib and midostaurin was assumed to hold.
Function with best Akaike's Information Criterion (AIC) fit	quizartinib: generalised gamma
Function with best Bayesian Information Criterion (BIC) fit	quizartinib: Gompertz
Function with best visual fit	quizartinib: log-normal
Function with the best fit according to external evidence	Not applicable

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	quizartinib: log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes – Applied at 3 years
Selected parametric function in base case analysis	quizartinib: log-normal
Validation of selected extrapolated curves	Because the cure-point was within the trial follow-up more emphasis was put on the fit statistical and visual fit during the trial follow up than long-term plausibility See Table 6 and Appendix D for the justification of the cure point

Figure 14 "Relapse from CRc" extrapolations used in base case

8.1.1.2 Extrapolation of Overall Survival after CRc (*CR1* to *Death*)

For quizartinib, the independent log-normal distribution was selected to obtain overall survival after CRc curves used in the base case analysis. See appendix D.2 and Table 25 for further description concerning how survival was extrapolated along with additional extrapolation curves and rationale for using the independent log normal distribution. Survival for midostaurin was estimated by applying the OS HR estimated from the MAIC to the quizartinib curve. Death from CRc adjusted for background mortality as well as survival post cure-point are shown in Figure 15. Based on NICE's assessment of midostaurin a two-fold standardized mortality rate (SMR) was applied to general population mortality post the cure-point.

Table 25 Summary of assumptions associated with extrapolation of "OS after CRc"

Method/approach	Description/assumption
Data input	Quizartinib: OS after CRc censored for HSCT from the weighted Q-F population ≤ 60 years matched to the RATIFY FLT3-ITD+ population Midostaurin: MAIC OS HR of 0.82 (0.48 – 1.39) applied to the quizartinib curve.
Model	Full parametrisation

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	Proportional hazard assumption between quizartinib and midostaurin was assumed to hold.
Function with best AIC fit	quizartinib: generalised gamma
Function with best BIC fit	quizartinib: exponential
Function with best visual fit	quizartinib: log-normal
Function with the best fit according to external evidence	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	quizartinib: log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes (3 years) – After the cure point the background mortality is applied adjusted using a standardized mortality rate of 2
Selected parametric function in base case analysis	log-normal
Validation of selected extrapolated curves	Because the cure-point was within the trial follow-up more emphasis was put on the fit statistical and visual fit during the trial follow up than long-term plausibility. See and Appendix D for the justification of the cure point

The resulting extrapolated curves for quizartinib and midostaurin of OS after CRc adjusted for background mortality are shown in Figure 15.

Figure 15 Death from CR extrapolations used in the base case

Abbreviations: CRc = Composite complete remission; HR = Hazard ratio; KM = Kaplan Meier;

8.1.2 Calculation of time constant transition probabilities (*Induction 1 & 2, First CR* and *1L HSCT*)

Time-constant TPs are used to estimate the share of patients achieving CR from induction treatment (*Induction* transition to *CR* and *Refractory*) as well as share of patients who are treated with HSCT after achieving a response (*CR* to *Allo-HSCT 1L*). Similarly time-constant TPs are used to estimate share of patients who relapse after HSCT 1L. Data from the

adjusted Q-F population ≤ 60 years matched to the RATIFY FLT3-ITD+ population was used to estimate time-constant TPs, with the exception of post HSCT 1L relapse rate where ITT data was used, as data was not available for the <60 population. Time-constant TPs from induction, CR and HSCT 1L are further specified in appendix N.1, N.2 and N.3 respectively

Table 26 Constant TP applied in the model (1L – adjusted population)

Transition (from to)	TPs(%)		Description of method and Reference
	quizartinib	midostaurin	
Induction 1 to Induction 1	Residual	Residual	-
Induction 1 to First CR	xx.x%	xx.x%	quizartinib: xx.x of xx.x patients had CRc within 28 days. Midostaurin: Applied CR OR vs quizartinib (1/0.92) See appendix N.1 for further details
Induction 1 to Refractory	xx.x%	xx.x%	quizartinib: xx.x of xx.x patients had refractory disease within 28 days. Midostaurin assumed =quizartinib See appendix N.1 for further details
Induction 1 to Dead	x.x%	x.x%	quizartinib: x.x of xx.x patients died within 28 days. Midostaurin assumed =quizartinib See appendix N.1 for further details
Induction 2 to Induction	0.00	0.00	All patients which require longer than 29 days to transition are moved out of induction at this cycle
Induction 2 to First CR	xx.x%	xx.x%	quizartinib: xx.x patients remaining in cycle 2, xx.x achieved CRc. Midostaurin: Applied CR OR vs quizartinib (1/0.92) See appendix N.1 for further details
Induction 2 to Refractory	Residual	Residual	-
Induction 2 to Dead	x.x%	x,x%	quizartinib: xx.x patients remaining in cycle 2, x.x died. Midostaurin assumed = quizartinib See appendix N.1 for further details
First CR to First CR	Residual	Residual	-
First CR to 1L Relapse	Time-varying	Time-varying	quizartinib: Relapse from CRc extrapolated for quizartinib (see section 8.1.1.1). Midostaurin: CIR HR applied to quizartinib curve (1/0.42)
First CR to HSCT	xx.x%	xx,x%	quizartinib: Based on ITT population as data not available for <60. TP is calculated by use of Excel "Solver" function. The function is used to set the TP so that the share of patients who move to HSCT equal the fraction of patients who underwent HSCT in Q-F. xx patients with protocol-specified HSCT after CRc out of 268 patients in the ITT analysis set in quizartinib arm midostaurin: Similar approach to quizartinib, using the "Solver function". In Stone et al., 2017. Transplantation was performed during the first complete remission in 28.1% of the patients in the midostaurin See appendix N.2 for further details
First CR to Dead (Time-varying)	Time-varying	Time-varying	quizartinib: Time to death from CRc censored by HSCT extrapolated for quizartinib (see

			section 8.1.1.2). Midostaurin: OS HR applied to quizartinib curve (1/0.82)
1L HSCT post recovery to relapse	x.xx%	x.xx%	quizartinib: Based on ITT population as data not available for <60, xx of xx patients who had HSCT relapsed over an average length of xxxx days. Midostaurin: Assumed equal to placebo arm in Q-F. Assuming time-invariant transitions, xx of xx patients relapsed after HSCT Dover an average length of xxx days. See appendix N.3 for further details

Source: ClinicalTrials.gov, 2016 (46); ClinicalTrials.gov, 2008 (9); Daiichi Sankyo, Inc., 2022 (8); Daiichi Sankyo, Inc., 2023 (7).

8.2 Presentation of efficacy data from the literature

Not applicable.

8.3 Modelling effects of subsequent treatments

8.3.1 Source of subsequent treatments efficacy data

The data from Q-F and RATIFY was insufficient to inform state transitions in later treatment lines. As a result, external literature has been used to estimate TPs from the health states *Relapse 1L*, *Relapse 2L, Complete Remission in 2L (CR2)* towards other health states. Similarly, mortality after having received HCT is based on external literature, where equal TPs have been assumed for HCT in 1L and 2L. TPs for the health states described here in section 8.3 do not differ between the quizartinib- and the midostaurin arm. Table 27 describes the TP values applied for health state following failure of 1L treatments and how these were calculated (with further details provided in appendix N.3, N.4 and N.5). The ADMIRAL trial was considered an appropriate source to inform efficacy data for these states as it is a Phase 3 study comparing gilteritinib to salvage chemotherapy in relapsed or refractory FLT3-mutated AML (57). See Table 131 in appendix N.5 for a comparison of key patient characteristics between Q-F and ADMIRAL.

Mortality data for patients having received allo-HSCT 2L was sourced from Styczynski et al., 2020 (59). This retrospective observational study analysed post-HSCT outcomes in AML, ALL, and CML patients (see appendix N.4 for further description of the study).

8.3.2 TP applied in the relapse, refractory, 2L CR and HSCT states

Table 27 Constant TP applied in the model (following failure of 1L treatments)

Transition (from to)	TPs (%) (all treatments)	Reference
Refractory to Refractory	Residual	-
Refractory to 2L CR	14,3%	ADMIRAL trial (Perl et al., 2019) 41 (31 patients received gilteritinib and 10 received salvage chemotherapy) of 146 patients (98 from gilteritinib arm and 48 from salvage chemotherapy arm) achieved a CR/CRh responding over 1.97 months (weighted average time to CRc in gilteritinib and in salvage chemotherapy arm)
Refractory to Dead	5,2%	ADMIRAL trial (Perl et al., 2019) 60-day mortality weighted by trial arm, assumed to be time-invariant and adjusted to TP for 28-day cycle length

Transition (from to)	TPs (%) (all treatments)	Reference
1L Relapse to 1L Relapse	Residual	-
1L Relapse to 2L CR	30,0%	ADMIRAL trial (Perl et al., 2019) 120 (103 patients received gilteritinib and 17 received salvage chemotherapy) patients of 225 patients (149 from gilteritinib arm and 76 from salvage chemotherapy arm) responding over 1.96 months (weighted average time to CRc in gilteritinib and in salvage chemotherapy arm).
1L Relapse to dead	5,2%	ADMIRAL trial (Perl et al., 2019) 60-day mortality weighted by trial arm, assumed to be time-constant and adjusted to TP for 28-day cycle length "
2L CR to 2L CR	Residual	-
2L CR to 2L Relapse	2,2%	ADMIRAL follow up (Perl et al., 2022). 2-year cumulative relapse rate in gilteritinib treated patients who achieved a best response of CR were 56.2%
2L CR to 2L HSCT	12,5%	ADMIRAL follow up (Perl et al., 2022). 355 patients (246 patients received gilteritinib and 109 received salvage chemotherapy) were included in the safety analysis set. 83 (64 from gilteritinib arm and 19 from salvage chemotherapy arm) underwent HSCT (23.4%), with the median follow-up of 37.1 months
2L CR to Dead	2,8%	ADMIRAL follow up (Perl et al., 2022). One year mortality weighted by trial arm. (62.1% in gilteritinib arm [n=247] and 83.2% in salvage chemotherapy arm [n=124]), assumed to be time-invariant and adjusted to 28-day cycle length
2L Relapse to 2L Relapse	Residual	-
2L Relapse to Dead	5,2%	Assumed the same as the 1L based on KOL validation
HSCT (1L/2L), tunnel state 1 to Dead	3.7%	Styczynski et al, 2020 Cohort 2, Figure 1a , 2,797 deaths out of 7,1494 patients over 30 days
HSCT (1L/2L, tunnel states 2-3 to Dead	4.2%	Styczynski et a l, 2020 Cohort 2, Figure 1b, 6,403 deaths out of 61,220 patients over 70 (100-30) days
HSCT recovery (1L/2L), tunnel states 1-10 to Dead	2.4%	Styczynski et al, 2020 Cohort 2, Figure 1c, 13,449 deaths out of 58,609 patients, over 265 (365-100) days
Post-HSCT recovery (1L/2L to Dead	0.4%	Styczynski et al, 2020 Cohort 2, Figure 1d, 7,527 deaths out of 37,487 patients, over four years (1,460 days)
2L HSCT maintenance to relapse	[redacted]	Assumed 50% higher than 1L based on KOL. Assumed = to placebo in Q-F.

Source: Styczynski (2020)(59) Perl (2019)(57) , Perl (2022)(58)

8.4 Other assumptions regarding efficacy in the model

Not relevant

8.5 Overview of modelled average treatment length and time in model health state

The model average (means and medians) of "Relapse from CRc" and "Death from CRc" censored for HSCT are shown in Table 28 alongside with the observed values from Q-F and RATIFY.

Table 28 Estimates in the model

	Modelled average* (years)	Modelled median * (years)	Observed median from relevant study (months)
Quizartinib Death from CRc‡	[redacted]	[redacted]	[redacted]
Midostaurin Death from CRc‡	[redacted]	[redacted]	[redacted]
Quizartinib Relapse from CRc‡	[redacted]	[redacted]	[redacted]
Midostaurin Relapse from CRc‡	[redacted]	[redacted]	[redacted]

Notes:* these values are to be find in the sheet Survival after CRc for RFS and Post-HSCT survival for OS, in cells CH11:CJ13. ¥ Q-F median follow-up: 39.2 months; RATIFY: Among patients who survived median follow-up time was 59 months.

In Table 29 is described the mean estimated duration in each model stage.

Table 29 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (years)

Treatment	Health states (months)			
	Treatment length	Induction	Refractory	First CR1
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]
	Relapse	CR2	Relapse 2	HSCT 1L
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]
	HSCT recovery 1L	Post HSCT 1L maintenance	Relapse after HSCT 1L	HSCT 2L
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]
	HSCT recovery 2L	Post HSCT 2L maintenance		
Quizartinib	[redacted]	[redacted]		
Midostaurin	[redacted]	[redacted]		

9. Safety

9.1 Safety data from the clinical documentation

Analysis of safety data for quizartinib and midostaurin was assessed based on Q-F and Ratify respectively. The safety population in Q-F includes all subjects who received at least one dose of study drug. In Q-F, AEs reported are treatment-emergent adverse events (TEAEs),. TEAEs are defined as AEs that occurred after the first dose of study drug or AEs that worsened in severity after the first dose of study drug and up to 30 days after the last dose of study drug. Related AEs occurring more than 30 days after the last dose of study drug were also considered TEAEs. Similarly, treatment-emergent SAEs are presented for Q-F. An SAE was an AE that resulted in either death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or was an important medical event

The safety population in RATIFY has not been specified in Stone et al., 2022 (2). In RATIFY, an AE was defined as an unfavourable change in the health of a participant that happens during a clinical study or within a certain amount of time after the study has ended. This change may or may not be caused by the intervention/treatment being studied (9). A clear definition of SAE was also not reported, nor was it clearly specified whether the events were treatment-emergent adverse events or any type of adverse event occurring during the trial.

An overview of safety events is presented in Table 30. The proportion of patients with ≥1 AEs and ≥ 1 CTCAE grade ≥ 3 were similar across the treatment arms in Q-F. However, more patients in the quizartinib arm than in the placebo arm experienced ≥ 1 treatment-emergent SAE, ≥ 1 treatment-related TEAE, had a dose reduction, and discontinued treatment due to AEs. Overall, the safety events were similar in Q-F and RATIFY, except from that more patient in the quizartinib arm discontinued treatment due to AEs compared to the other treatment arms. One should however interpret results between the quizartinib arm and midostaurin arm directly with caution as definitions of adverse event may differ between trials, particularly with respect to the difference between treatment-emergent adverse event (Q-F) compared to adverse event (RATIFY). Evaluating the safety profile by assessing quizartinib and midostaurin against their respective placebo arms eliminates this bias

Table 30 Overview of safety events (Q-F<60 [13-08-2021] and RATIFY [July 2016])

	Q-F Quizartinib (N=159)	Q-F Placebo (N=160)	RATIFY Midostaurin (N=360)	RATIFY Placebo (N=357)
Number of AEs, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥1 AEs, n (%)	159 (100.0)	159 (99.4)	321/355[c] (90.42)[d]	324/354[c] (91.53)[d]
Number of SAEs*, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 SAEs*, n (%)	84 (52.8)	64 (40.0)	157/355[c] (44.23)	154/354[c] (43.50)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A	N/A

	Q-F Quizartinib (N=159)	Q-F Placebo (N=160)	RATIFY Midostaurin (N=360)	RATIFY Placebo (N=357)
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	145 (91.2)	142 (88.8)	N/A	N/A
Number of adverse reactions, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	34 (21.4)[b]	10 (6.3)[b]	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment due to AEs, n (%)	26 (16.4)	11 (6.9)	11 (3.1)	5 (1.3)

Notes: * A SAE is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). [§] CTCAE v. 5.0 must be used if available. [a] Number and proportion with treatment-related TEAE. [b] Number and proportion with dose reduction associated with TEAE. [c] Number affect / number at risk. [d] Not including SAEs.
Source: Daiichi Sankyo, 2022, table 14.3.1.6.1 (8); European Medicines Agency, 2027 (69); ClinicalTrials.gov, 2008 (9).

Table 31 presents an overview of treatment-emergent SAEs in Q-F (8) and SAEs RATIFY (9). SAEs were similar both within the two treatment arms of Q-F and within the two treatment arms of RATIFY. For instance, the percentage of patients with an event of febrile neutropenia, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, neutrophil count decreased, and platelet count decreased.

Table 31 Serious adverse events (Q-F<60 [13-08-2021] and RATIFY [July 2016])

SAEs	Quizartinib (N=159) (TE-SAE)		Placebo (N=160) (TE-SAE)		Midostaurin (N=355) (SAE)		Placebo (N=354) (SAE)	
	No. with SAEs (%)	No. of SAEs	No. with SAEs (%)	No. of SAEs	No. with SAEs (%)	No. of SAEs	No. with SAEs (%)	No. of SAEs
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	25 (7.04)	32	35 (9.89)	39
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	105 (29.58)	144	110 (31.07)	152
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	23 (6.48)	27	16 (4.52)	17
Haemoglobin decreased	[redacted]	[redacted]	[redacted]	[redacted]	154 (43.38)	237	148 (41.81)	230
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	89 (25.07)	111	89 (25.14)	108
Ear, nose, and throat examination abnormal	[redacted]	[redacted]	[redacted]	[redacted]	40 (11.27)	52	42 (11.86)	54
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	98 (27.61)	149	91 (25.71)	126
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	70 (19.72)	101	65 (18.36)	86
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	95 (26.76)	136	98 (27.68)	130
Fever	[redacted]	[redacted]	[redacted]	[redacted]	34 (9.58)	38	33 (9.32)	38
Pain	[redacted]	[redacted]	[redacted]	[redacted]	14 (3.94)	17	18 (5.08)	24
Catheter site infection (Q-F)/Catheter related infection (RATIFY)	[redacted]	[redacted]	[redacted]	[redacted]	29 (8.17)	39	21 (5.93)	26
Infection	[redacted]	[redacted]	[redacted]	[redacted]	30 (8.45)	41	26 (7.34)	33
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	35 (9.86)	41	35 (9.89)	41
Alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]	8 (2.25)	8	20 (5.65)	24
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	30 (8.45)	33	29 (8.19)	32
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]	25 (7.04)	32	36 (10.17)	42

SAEs	Quizartinib (N=159) (TE-SAE)		Placebo (N=160) (TE-SAE)		Midostaurin (N=355) (SAE)		Placebo (N=354) (SAE)	
Electrocardiogram QTc interval prolonged	[redacted]	[redacted]	[redacted]	[redacted]	17 (4.79)	22	19 (5.37)	22
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	19 (5.35)	25	22 (6.21)	32
Laboratory test abnormal	[redacted]	[redacted]	[redacted]	[redacted]	18 (5.07)	33	28 (7.91)	47
Leukocyte count decreased	[redacted]	[redacted]	[redacted]	[redacted]	41 (11.55)	66	47 (13.28)	78
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]	[redacted]	22 (6.20)	30	36 (10.17)	56
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	145 (40.85)	227	146 (41.24)	224
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	155 (43.66)	239	146 (41.24)	227
Anorexia	[redacted]	[redacted]	[redacted]	[redacted]	21 (5.92)	30	26 (7.34)	29
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]	17 (4.79)	23	22 (6.21)	31
Serum albumin decreased	[redacted]	[redacted]	[redacted]	[redacted]	19 (5.35)	28	22 (6.21)	26
Serum calcium decreased	[redacted]	[redacted]	[redacted]	[redacted]	20 (5.63)	25	26 (7.34)	30
Serum potassium decreased	[redacted]	[redacted]	[redacted]	[redacted]	31 (8.73)	37	47 (13.28)	53
Serum sodium decreased	[redacted]	[redacted]	[redacted]	[redacted]	20 (5.63)	22	20 (5.65)	22
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	19 (5.35)	23	20 (5.65)	25
Headache	[redacted]	[redacted]	[redacted]	[redacted]	41 (11.55)	54	42 (11.86)	63
Cough	[redacted]	[redacted]	[redacted]	[redacted]	17 (4.79)	21	19 (5.37)	20
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	20 (5.63)	22	24 (6.78)	24
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]	24 (6.76)	26	22 (6.21)	24
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	27 (7.61)	28	17 (4.80)	19
Petechiae	[redacted]	[redacted]	[redacted]	[redacted]	35 (9.86)	45	34 (9.60)	52

SAEs	Quizartinib (N=159) (TE-SAE)		Placebo (N=160) (TE-SAE)		Midostaurin (N=355) (SAE)		Placebo (N=354) (SAE)	
Rash desquamating	[redacted]	[redacted]	[redacted]	[redacted]	59 (16.62)	70	66 (18.64)	71
Skin disorder	[redacted]	[redacted]	[redacted]	[redacted]	23 (6.48)	28	23 (6.50)	30
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	25 (7.04)	26	19 (5.37)	22

Note: Ω Defined as a TEAE in Q-F and not a SAE. ‡ Defined as an AE in Q-F and not a SAE. * A SAE is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).Source: Daiichi Sankyo, 2022, Table 14.3.2.1.4 (8); ClinicalTrials.gov, 2008 (9).

Table 32 provides list of the AEs included in the health economic analysis. AEs of grade ≥3 occurring with an incidence of ≥5% were included in the health economic analysis, in alignment with previous AML submissions (4). AEs were assumed to occur within the first cycle of the model. Incidence rates for AEs (specifically, for TEAEs) for the quizartinib and SC regimens were sourced from the Q-F trial (8) and the AE rates for midostaurin regimens were sourced from RATIFY (60).

Table 32 Adverse events used in the health economic model

Adverse events	Quizartinib (159)	Midostaurin	Source and Justification
Anaemia	5.7%	92.7%	For quizartinib, grade ≥3 TEAEs that occurred in ≥ 5% of patients in Q-F trial. For midostaurin, grade 3, 4 or 5 AEs that occurred in ≥ 5% of patients in midostaurin arm in RATIFY reported in Stone et al., 2017 (2).For midostaurin, grade 3, 4 or 5 AEs that occurred in ≥ 5% of patients in midostaurin arm in RATIFY reported in Stone et al., 2017 (2).
Diarrhoea	3.8%	15.8%	
Fatigue	0.6%	9.0%	
Febrile neutropenia	45.3%	81.7%	
Thrombocytopenia	8.2%		
Hyperbilirubinemia	[redacted]	7.0%	
Hypocalcaemia	0.0%	6.8%	
Hypokalaemia	17.0%	13.8%	
Hyponatraemia	[redacted]	8.7%	
Hypophosphataemia	5.7%	5.4%	
Increased alanine aminotransferase	4.4%	12.7%	
Infection*	[redacted]	52.4%	
Leukopenia	[redacted]	26.2%	
Lymphopenia	[redacted]	19.2%	
Mucositis or stomatitis	5.0%	6.2%	
Nausea	0.6%	5.6%	
Neutropenia	17.6%	95.2%	
Pain	[redacted]	13.2%	
Pneumonia	[redacted]	N/A	
Pneumonitis or pulmonary infiltrates	N/A	7.9%	
Rash or desquamation	2.5%	14.1%	
Thrombocytopenia	8.2%	97.5%	
Neutrophil count decreased	11.3%	0.0%	
Sepsis	4.4%	0.0%	
Gamma-glutamyl transferase increased	[redacted]	0.0%	
Platelet count decreased	[redacted]	0.0%	
Hypertension	4.4%	0.0%	
GVHD*	1.3%	39.0%	

Notes: * as system organ class level. * assumed = to ITT population: GVHD during the HSCT period in subjects who underwent protocol-specified HSCT
Source: Daiichi Sankyo, 2022, (8); Stone et al. 2017 (2).

9.2 Safety data from external literature applied in the health economic model

For clarity and conciseness, this information is included in section 9.1 alongside data from the clinical documentation.

10. Documentation of health-related quality of life (HRQoL)

Patient reported outcomes (PRO)s for exploratory purposes were collected using EuroQoL EQ-5D-5L in the Q-F study (6), and was included in this assessment following the DMC current method guide.

Table 33: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Q-F	Utility values for induction, first remission, relapses and refractory health states in the economic model. For other health states Q-F EQ-5D values were adjusted with assumptions based on published literature.

Source: Source: Daiichi Sankyo 2023 (8); Midostaurin NICE TA 523.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

Despite the study was not designed to formally compare the treatment impact of quizartinib on PRO measures to that of placebo when combined with SC, the results provide an interesting insight into trends in QoL within this patient population. Given the exploratory nature of the PRO analyses, the results should be interpreted carefully.

10.1.2 Data collection

The EQ-5D-5L scores were collected at each trial visit for both treatment arms. The population contributing to HRQoL data include all subjects in the <60 analysis set who completed the relevant EQ-5D-5L on day 8 of the induction phase cycle 1 (i.e., PRO baseline). For the subpopulation with age < 60, a total of [redacted] subjects were included in the ITT analysis set. Among them, [redacted] ([redacted]%) subjects were included in the PRO Analysis Set ([redacted] for quizartinib and placebo arm). (6). HRQoL data for the ITT population are shown in Appendix L, section L.4.3.

Overall, the completion rates for both QoL scales were high and patients in both arms reported similar QoL scores at PRO baseline. Minimal differences were observed between the two treatment arms in score changes from baseline and were not statistically significant as seen in the longitudinal model (MMRM). At the item level, missing responses were managed as per the scoring manual. For the EQ-5D-5L, missing data were not imputed or replaced for individual items or the VAS. For the longitudinal modelling, missing data were handled under the missing-at-random (MAR) assumption in the MMRM model (6).

The pattern of missing data and completion from the EQ-5D-5L index score (Denmark value set) over time is demonstrated in Table 34.

Table 34 Pattern of missing data and completion (<60 population)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Induction Cycle 1 Day 8	[redacted]	[redacted]	[redacted]	[redacted]
Induction Cycle 1 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Induction Cycle 2 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle1 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle1 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle2 Day 6	[redacted]	[redacted]	[redacted]	[redacted]

Consolidation Cycle2 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle3 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle3 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle4 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Cycle4 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle1 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle31 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Continuation Cycle34 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]

Source: Daiichi Sankyo, 2024, table 4.4.4a (63).

10.1.3 HRQoL results

An MMRM analysis was performed adjusting for score at baseline, treatment, time, and a treatment-by-time interaction. It shows the change from PRO baseline effect of quizartinib vs. placebo on the EQ-5D-5L index score (DK value set) over time. The results demonstrate an improvement in EQ-5D-5L index score (DK value set) over time in both treatment arms compared to PRO baseline results. This data is presented in Table 35. Figure 16 display the mean change from baseline for both quizartinib and placebo.

Figure 16 EQ-5D-5L DK index score - Plot of Least Square Means estimate by treatment across time. Data cutoff 13 Aug 2021. PRO, ITT Analysis Set, Q-F population < 60 .

Notes: Least Square Means and associated Confidence Interval from Mixed Model Repeated Measures: Changes in the QoL scores = Baseline + Treatment + Time + Treatment x Time with a AR (1) structure of covariance matrix for residuals. The X-axis reports visits where PRO data was gathered in accordance with Table 34 and Table 35
Source: Daiichi Sankyo 2023 (8)

Table 35 HRQoL EQ-5D-5L summary statistics, Q-F < 60

	Quizartinib (N 254) Mean [95% CI)	Num-ber of pa-tients	Placebo (N=255) Mean [95% CI)	Number of pa-tients	Quizartinib vs. placebo [95% CI)
	Mean, [95% CI][a]		Mean, [95% CI][a]		Difference (95% CI) [a]
Induction Cycle 1 Day 28					
Induction Cycle 2 Day 28					
Consolidation Cycle 1 Day 6					
Consolidation Cycle 1 Day 28					
Consolidation Cycle 2 Day 6					
Consolidation Cycle 2 Day 28					
Consolidation Cycle 3 Day 6					
Consolidation Cycle 3 Day 28					
Consolidation Cycle 4 Day 6					
Consolidation Cycle 4 Day 28					
Maintenance Cycle 1 Day 1					
Maintenance Cycle 4 Day 1					
Maintenance Cycle 7 Day 1					
Maintenance Cycle 10 Day 1					
Maintenance Cycle 13 Day 1					
Maintenance Cycle 16 Day 1					
Maintenance Cycle 19 Day 1					
Maintenance Cycle 22 Day 1					
Maintenance Cycle 25 Day 1					
Maintenance Cycle 28 Day 1					
Maintenance Cycle 31 Day 1					
Maintenance Cycle 34 Day 1					

Notes: a = Least Square Means and associated Confidence Interval from Mixed Model Repeated Measure
Source: Daiichi Sankyo 2023, table 4.4.4b (63).

10.2 Health state utility values (HSUVs used in the health economic model)

The utility used in the model were derived from the Q-F population of age < 60 in alignment with clinical data. A scenario using the overall population values was conducted in the Naïve scenario. As there was no statistically significant difference across treatment arms, an overall health state utility was applied in the model. Mean patient level utility values were derived for induction, first remission consolidation, first remission continuation, relapse after first remission, refractory, and protocol specify HSCT after first remission (Table 36). As trial data could not provide values for all the health states, an SLR was conducted to identify published literature that characterises the impact of FLT3+ AML on HRQoL, the details of which are described in Appendix I.

10.2.1 HSUV calculation

EQ-5D-5L and Danish preference weights were used. In the health economic model, utilities were age-adjusted according to section 7.3 of the DMC methods guide.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

The disutility was not separately considered for AEs because the health state utility values used in the model are assumed to incorporate the impact of AEs experienced during treatment. This approach is based on the approach used in NICE TA523 for midostaurin (31). The only disutility incorporated in the model was for GVHD (see Table 36).

10.2.3 HSUV results

The health state utility values applied in the base case and the source data used are described in Table 36.

Table 36 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff used	Comments
Health state utilities				
Induction	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms of Q-F.
First remission consolidation	[redacted]			Estimate is based on mean of both trial arms of Q-F.
First remission continuation and First CR	[redacted]			Estimate is based on mean of both trial arms of Q-F.
Relapse after first remission	[redacted]			Estimate is based on mean of both trial arms of Q-F.
Refractory	[redacted]			Estimate is based on mean of both trial arms Q-F.

Second CR	[redacted]			90% of the value for First CR
Relapse 2	[redacted]			90% of the Relapse 1L value
HSCT treatment 1L	0.613 [0.362, 0.835]	EQ-5D	Not specified	Estimates were derived from NICE TA 523
HSCT recovery 1L	0.810 [0.405, 0.995]			
HSCT maintenance 1L	0.826 [0.401, 0.998]			
HSCT treatment 2L	0.552 [0.333, 0.760]			90% of the 1L health state. KOL opinion
HSCT recovery 2L	0.729 [0.403, 0.952]			90% of the 1L health state. KOL opinion
HSCT maintenance 2L	0.743 [0.406, 0.963]			90% of the 1L health state. KOL opinion
Disutility				
GVHD	0.173 [0.111, 0.2456] *			Values used in NICE TA 523

Notes: Calculated based on a standard error of 0.03

Source: Daiichi Sankyo 2023 (8); Midostaurin NICE TA 523).

10.3 Other trials than the clinical trials forming the basis for relative efficacy

In the absence of Q-F data, utilities for HSCT treatment, recovery, and post-HSCT maintenance were derived from the midostaurin NICE TA 523 (31), which leveraged QLQ-30 data from Grulke, et al. 2012 (55) mapped into EQ-5D. The disutilities applied to GVHD were also picked from NICE TA 523, originally referencing Peric (2016) (70).In the absence of Q-F data, utilities for HSCT treatment, recovery, and post-HSCT maintenance were derived from the midostaurin NICE TA 523 (31), which leveraged QLQ-30 data from Grulke, et al. 2012 (55) mapped into EQ-5D. The disutilities applied to GVHD were also picked from NICE TA 523, originally referencing Peric (2016) (70).(70).

10.3.1 Study design

The midostaurin NICE TA 523 describes the health economic analysis supporting the submission for midostaurin in the UK. The model used to conduct the economic analysis was a 3-health state partitioned survival model including 5 health states: induction, complete remission, relapse, HSCT, and death. The HSCT health state was splitter into 3 tunnel states (treatment, recovery, and post HSCT].

10.3.2 Data collection

The data collection process to support the economic analysis is not described in detail in the NICE TA 523 documents. The analysis includes both data sourced from the submitting company and from the ERG group.

10.3.3 HRQoL Results

The utility values included in the economic evaluation are described below in Table 37.

10.3.4 HSUV and disutility results

The utility values included in the economic evaluation are described below in Table 37.

Table 37 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set] used	Comments
HSCT utility values				
NICE TA 523	0.613	EQ-5D	Not specified	HSCT treatment 1L: EORTC QLQ-C30 data mapped into EQ-5D
NICE TA 523	0.810			HSCT recovery 1L: EORTC QLQ-C30 data mapped into EQ-5D*
NICE TA 523	0.826			HSCT maintenance 1L: EORTC QLQ-C30 data mapped into EQ-5D*
Disutility GVHD				
NICE TA 523	0.173	EQ-5D	Not specified	ERG recommended values for GVHD disutility

Source: Midostaurin NICE TA 523 (31) leveraging values from (Grulke, et al. 2012 (55)] using the algorithm developed by Crott, et al. (2010] (56). Source: Midostaurin NICE TA 523 (31) leveraging values from (Grulke, et al. 2012 (55)] using the algorithm developed by Crott, et al. (2010] (56).

11. Resource use and associated costs

Costs included in the analysis were: drug costs, hospitalisations, outpatient visits, stem cell transplantation, adverse events and patient time and transportations costs (for all, where possible, costing is based on DRG rates).

Cost of SC were assumed to be covered by the DRGs, in line with the assumptions taken in the midostaurin Danish cost analysis (47), while the costs of quizartinib and midostaurin were added separately. Similarly, for subsequent treatments the cost of FLAG-Ida was also assumed to be covered by the DRG, as suggested by DMC in the previous review of the quizartinib for FLT3-ITD+ submission. The cost of gilterinib and sorafenib were instead added separately, as these are oral treatments and may continue beyond the time of hospitalisation.

11.1 Medicine costs quizartinib and midostaurin regimens

The costs are pharmacy purchase price or Apotekernes indkøbspris (AIP), derived from Medicinpriser.dk (44) and calculated for quizartinib based on the expected AIP.

RDI for quizartinib was [redacted]% in induction, [redacted]% in consolidation and [redacted]% in maintenance. An overall RDI of 95% for Midostaurin was based on NICE TA523 (31)

Table 38 Pharmaceutical costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	AIP [DKK]
Quizartinib	18 mg * 28	See Section 3.4		N/A	51 203
	27 mg * 56			N/A	102 407
Midostaurin	25 mg * 56	See Section 3.5		N/A	43,538.12

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	AIP [DKK]
	25 mg* 112			N/A	87,076.23

Source: Medicinpriser.dk (44).

The mean duration of treatment applied in the model is summarised in Table 39. For quizartinib, the analysis of mean treatment duration was based on the safety analysis set, rather than the >60 population used to estimate efficacy against midostaurin, as the former is more resemblant of the patients seen in Danish clinical practice. This approach was therefore deemed more appropriate to estimate the treatment duration that would occur in the event of recommendation by the DMC.

As shown by Figure 7, some patients were still receiving maintenance treatment with quizartinib by end of follow-up. Internal analysis of IPD conducted by Daiichi Sankyo Nordics found that [redacted] out of [redacted] patients ([redacted]%) had not completed maintenance by end of follow-up. Among these "non-completers", mean number of maintenance cycles received were [redacted], whereas average number of cycles were [redacted] among those who finished treatment during trial follow-up. To account for additional drug acquisition costs resulting from "non-completers", a sensitivity analysis is conducted where it is assumed that these patients receive 50% of the additional cycles they can maximally receive. This results in an increase of [redacted] maintenance cycles for the quizartinib arm ([redacted] * [redacted] * ([redacted] – [redacted])). The Excel model associated with this dossier allows for the adjustment of this assumption.

For midostaurin, mean treatment duration is not publicly available. It is therefore assumed that mean treatment duration in induction and consolidation phases are similar to the quizartinib regimen given that midostaurin and quizartinib are both FLT3i treatments. The median duration of exposure in maintenance from the midostaurin SmPC was used to inform mean time on treatment for the midostaurin regimen in the maintenance phase.

Table 39 Mean treatment duration applied in the model (28 days cycles)

Mean treatment duration (28 days cycles)	quizartinib	midostaurin
Induction	x.xx	x.xx
Consolidation	x.xx	x.xx
Maintenance	xx.xx	11.96
HSCT recovery	10.00	0.00
Maintenance, post HSCT	x.xx	0.00
Total pre HSCT	xx.xx	15.05
Total post HSCT	xx.xx	8.65*

Abbreviations: HSCT = Hematopoietic stem cell transplantation
Notes: midostaurin induction and consolidation values were assumed equal to quizartinib. *In the midostaurin arm, sorafenib is administered as post HSCT maintenance, as per current treatment guidelines (29).
Source: CSR table 14.1.5. unadjusted (8), NICE TA523 (31), Burchert (2020) (60)Source: CSR table 14.1.5. unadjusted (8), NICE TA523 (31), Burchert (2020) (60)

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

Administration costs are not included in the economic analysis as they assumed to be covered by the DRG as assumed in the midostaurin Danish cost analysis (47) (SC will be administered in hospital, and the oral treatment will also be initiated while hospitalised).

11.4 Disease management costs

Disease management costs were included in the model to account for the routine monitoring visits and procedures which occur during AML patient's treatment pathway. For induction and consolidation, health state resource used was derived by the Danish midostaurin cost analysis, (47). For this analysis, it was assumed that health care resource use did not differ between 1L and 2L CR and relapse. In addition, resource use in refractory disease was assumed equal to relapse. As the midostaurin cost analysis did not report frequencies for the maintenance state, internal experts within Daiichi Sankyo were consulted who reported that patients usually have one outpatient visit per cycle in the maintenance phase. The frequency of resource use for disease management items, by health state in days per cycle, are presented in Table 40.

Table 40 Frequency of resource used per health state

Health state	Hospital days	Daytime admission	Outpatient visit
Induction	22	2	6.5
Consolidation	10	1	12
Maintenance	0	0	1
Relapse 1L, 2L and refractory	23	2	8
CR1, CR2	0	0	0.5

Source: midostaurin cost analysis (47) and assumptions

The unit costs, presented in Table 41, were aligned with the ones used in the midostaurin cost analysis and sourced from the Danish DRG list 2024 and the Takstsystem 2024 Vejledning. When the length of hospitalisation exceeded the DRG trim points reported in Table 41, the extra daily cost for hospitalisation per day was added, in alignment with the Danish midostaurin cost analysis (47).

Table 41 Unit costs of resource used per health state

DRG	Description	Cost (DKK)	DRG trim day	Applied to
17MP03	Højdosis kemoterapi u. stamcellestøtte, pat. mindst 18 år	65,737	8	Hospitalisation in induction
17MP11	Kompleks kemoterapi på svulster i lymfatisk og bloddannende væv, pat. mindst 18 år	44,064	7	Hospitalisation in other health states then induction
16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år	2,111	1	Daytime admission in any health state

N/A	Takstvejledning_2024 p 16	2,316	N/A	Extra daily cost of hospitalisation -all health states

Source: midostaurin cost analysis (47) and assumptions

ECG regular monitoring is required for patients in treatment with quizartinib, and only in patients concurrently receiving medicinal products that can prolong the QT interval in those treated with midostaurin according to their respective SmPC (43) (71). The ECG were also assumed to be conducted while the patients is hospitalised.

11.4.1 Stem cell transplantation costs

HSCT procedure costs were included in the analysis with a unit cost of 904,674 (DRG 26MP22 allogen stemceltransplantation) (72). The HSCT cost, either in 1L or 2L, is added as one-off once patients enter the first HSCT tunnel state.

For the health state following HSCT (HSCT recovery and maintenance), resource consumption was also derived from the Danish midostaurin cost analysis, reporting weekly outpatients' visits in HSCT recovery and one visit every two months while in post HSCT maintenance. Complications related to HSCT (as GVHD) were covered by the cost of AE (see following section). Resource consumption was assumed equal between 1L and 2L HSCT.

11.5 Costs associated with management of adverse events

AE unit costs were multiplied by the percentage of patients who experienced each of the AE (presented in Section 9) and applied as one-off cost in the first cycle of the model as a simplifying assumption, as these are expected to be temporary and not recurring costs. In addition, the cost of GVHD was included for patients experiencing this SAE after HSCT as major complication that can occur during transplantation.

Table 42 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Anemia	Anemia UNS, 16MA98, code: DD649	2,111
Diarrhea	Non-infectious diarrhea UNS, 06MA11, code: DK529B	7,818
Fatigue	Sequela with fatigue after cancer treatment, 21MA07, code: DT983D5	19,050
Febrile neutropenia	Neutropenia UNS, 16MA98, code: DD709	2,111
Hyperbilirubinemia	Hyperbilirubinemia type 2, 07MA98, code: DE806A	1,947
Hypocalcemia	Anden abnorm blodprøve, DR798	4,728
Hypokalemia	Hypokalaemia, 10MA98, code: DE876	1,847
Hyponatremia	Hyponatremia, 10MA98, code: DE871A	1,847
Hypophosphatemia	Hypophosphatemia, 10MA98, code: DE833A	1,847
Increased alanine aminotransferase	Anden abnorm blodprøve, DR798	4,728
Infection	Bakteriæl infektion, 18MA98	2,570
Leukopenia	Leukopenia, 16MA98, code: DD728H	1,947
Lymphopenia	Lymphopenia, 16MA98 , code: DD728D	1,947

	DRG code	Unit cost/DRG tariff
Mucositis or stomatitis	Stomatistis UNS, 03MA98, code: DK121B	2,107
Nausea	Nausea and vomitting, 06MA11, code: DR119	7,818
Neutropenia	Neutropenia UNS, 16MA98, code: DD709	1,947
Pain	Pain UNS, 23MA03, code: DR529	5,103
Pneumonitis or pulmonary infiltrates	Pneumonia UNS, 04MA98, code: DJ189	1,311
Rash or desquamation	Rash UNS, 09MA98, code: DR219	1,625
Thrombocytopenia	Thrombocytopenia UNS, 16MA98, DD696	1,947
GVHD (post-HSCT event]	Graft-versus-host reaction, 16MA98, DT860A	1,947
Neutrophil count decreased	Assumed as Neutropenia UNS, 16MA98, code: DD709	1,947
Sepsis	Assumed as Neutropenia UNS, 16MA98, code: DD709	2,570
Gamma-glutamyl transferase increased	Anden abnorm blodprøve, DR798	4,728
Platelet count decreased	Anden abnorm blodprøve, DR798	4,728
Hypertension	Assumed as Anemia UNS, 16MA98, code: DD649	2,111

Source: DRG Takster (72).

11.6 Subsequent treatment costs

The subsequent treatments included in the model were FLAG-Ida and gilteritinib which are applied to the health states *Relapse 1L* and *Refractory*. It was assumed that 60% and 40% of patients were treated with Flag-IDA and gilterinib respectively in the quizartinib arm whereas it was assumed to be 40% and 60% for the midostaurin arm.

Based on advise from the DMC, the pharmaceutical cost of FLAG-Ida is assumed to be covered by the DRG unit cost applied (17MP03) along with administration- and hospitalisation cost. The pharmaceutical cost of gilterinib is instead added to this as oral therapy. using drug acquisition costs from Medicinpriser.dk.

The median treatment duration of treatment with gilteritinib from ADMIRAL was used to in the analysis, which was 5 treatment cycles (58). The median RDI of gilteritinib (98.45%) applied in the model was also sourced from the ADMIRAL trial based on the patients treated with gilterinib for >12 months.

Danish KOL have reported that sorafenib is often used as maintenance treatment option for FLT3-ITD+ AML post HSCT despite not currently being reimbursed (32). The cost of sorafenib was therefore included for patients post-HSCT maintenance in the midostaurin arm, assuming equal efficacy between quizartinib and sorafenib. Average duration of treatment was assumed to be 8.65 cycles based on the SORMAIN study (60).

Table 43 Pharmaceutical costs of subsequent treatments

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment (in cycles]
Gilterinib	40 mg	84	113,065	98%	5.00
Sorafenib	200 mg	112	17,438.48	100%	8.65

Source: Medicinpricer.dk (44).

The dosing schedule for gilterinib (Table 44) was assumed to be the same for the refractory, relapse1, and post-HSCT relapse states across all treatment arms. The distribution of treatments is dependent on the 1L treatment regimen received. Patients in the midostaurin arm are assumed to receive sorafenib post HSCT. The dosage for sorafenib post HSCT received by patients in the midostaurin arm were sourced from the SORMAIN study (60).

Table 44 Subsequent treatments dosing schedule

Pharmaceutical	Dosing schedule	Administration	Treatment distribution
Gilterinib	120 mg/day; Once daily for 18 weeks (4.5 cycles]	Oral	quizartinib: 40% midostaurin: 60%
Sorafenib	400 mg/day (Day 1 until Day14: 400 mg/day 600 mg/day (Day 15 to Day 42) 800 mg/day (From Day 43 and after)	Oral	quizartinib: 0% midostaurin: 100% in post HSCT

Notes: Each cycle is 28 days in duration. For sorafenib, days are counted from the start of the treatment, which is assumed to be when patients enter the post-HSCT health state

Source: Perl et al. 2019 (57); Burchert 2020 (60).Source: Perl et al. 2019 (57).

11.7 Patient costs

11.7.1 Transportation costs

One round trip was included in the analysis for each resource consumption (hospitalisation, daytime admission and outpatient visit), regardless of the length of stay. The resources use was considered mutually exclusive. For HSCT procedure, transportation cost was applied at entry of HSCT health state, in alignment with the cost of the procedure. For AE, transportation costs were included as one-off costs in the first cycle. In addition, a round trip was included throughout the time horizon for patients experiencing GVHD. The cost of transportation (140 DKK per round trip) was sourced from the unit cost catalogue v 1.8 (73).

11.7.2 Patient time

The assumptions around the time needed for each resource use is described in Table 45. A unit cost of 188 DKK was used for all patient hours spent on treatment-related activities (73). Similarly to procedure and transportation cost, time cost for HSCT was included as one-off at entry of HSCT health state.

Table 45. Patients' time per resource use

Resource	Time per unit of resource	Assumptions and references
Hospitalisation (hours per day)	24 h	One entire day assumed; no additional time assumed for travel
Daytime admission (hours per visit)	8 h	Assumed 8 hours including travel
Outpatients visit (hours)	3 h	Assumed 3h including travel
Time for HSCT	21 days	HSCT length of stay varies between 14-21 days, Sundheds.dk (74)
AE	24 hours	Based on average of trim point for DRGs used to cost AE (resulting in one day hospitalisation)

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Genetic testing cost was included in the model in the induction phase to test patients' eligibility for treatment. The cost for genetic testing was derived from the Rigshospitalet's laboratory price list (Myelodysplastic syndrome-rel. gene; variation) with a unit cost of 6000 DKK.

12. Results

12.1 Base case overview

An overview of the base case is provided in Table 46.

Table 46 Base case overview

Feature	Description
Comparator	midostaurin
Type of model	Semi-Markov Model
Time horizon	53 years (lifetime]
Treatment line	1st line. Subsequent treatment lines included
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in Q-F (< 60 age) study based on Danish population weights (6), integrated with values from the literature used in previous NICE submission in AML (31).
Costs included	Pharmaceutical costs Disease management (health care resource use) costs including HSCT procedure Costs of adverse events Subsequent treatment costs Patients time and transportation FLT3-ITD+ genetic testing
Dosage of pharmaceutical	Quizartinib is administered orally. The dosage depends on treatment phase: induction and consolidation:40 mg daily; maintenance 30mg daily the first 15 days, 60 mg daily afterward.
Average time on treatment	Quizartinib: [redacted] years Midostaurin: [redacted] years

Feature	Description	
Parametric function for RFS	Quizartinib: Log-normal Midostaurin: Single HR vs quizartinib (HR = 1/0.42]	
Parametric function for OS	Quizartinib: Log-normal Midostaurin: Single HR vs quizartinib (HR = 1/0.82]	
Inclusion of waste	Yes	
Cure approach	From year 3	
Average time in model health state	quizartinib	midostaurin
Induction	[redacted]	[redacted]
Refractory	[redacted]	[redacted]
First CR	[redacted]	[redacted]
Relapse 1L	[redacted]	[redacted]
Second CR	[redacted]	[redacted]
Relapse 2	[redacted]	[redacted]
HSCT 1L	[redacted]	[redacted]
HSCT recovery 1L	[redacted]	[redacted]
Post HSCT 1L maintenance	[redacted]	[redacted]
HSCT relapse 1L	[redacted]	[redacted]
HSCT 2L	[redacted]	[redacted]
HSCT recovery 2L	[redacted]	[redacted]
Post HSCT maintenance 2L	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]

12.1.1 Base case results

Table 47 Base case results, discounted estimates

	quizartinib	midostaurin	Difference
Costs			
Drug Acquisition Costs	[redacted]	[redacted]	[redacted]
Drug Administration Costs	[redacted]	[redacted]	[redacted]
Adverse Event Costs	[redacted]	[redacted]	[redacted]
Disease Management Costs	[redacted]	[redacted]	[redacted]
Subsequent treatment Costs	[redacted]	[redacted]	[redacted]
Patient and transportation cost	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Life years gained			
Induction	[redacted]	[redacted]	[redacted]
Refractory	[redacted]	[redacted]	[redacted]

	quizartinib	midostaurin	Difference
CR 1L	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]
CR 2L	[redacted]	[redacted]	[redacted]
Relapse 2L	[redacted]	[redacted]	[redacted]
HSCT 1L	[redacted]	[redacted]	[redacted]
HSCT recovery 1L	[redacted]	[redacted]	[redacted]
Post HSCT 1L maintenance	[redacted]	[redacted]	[redacted]
Health state: Relapse after HSCT 1L	[redacted]	[redacted]	[redacted]
HSCT 2L	[redacted]	[redacted]	[redacted]
HSCT recovery 2L	[redacted]	[redacted]	[redacted]
Post HSCT 2L maintenance	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALY gained			
Induction	[redacted]	[redacted]	[redacted]
Refractory	[redacted]	[redacted]	[redacted]
CR 1L	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]
CR 2L	[redacted]	[redacted]	[redacted]
Relapse 2L	[redacted]	[redacted]	[redacted]
HSCT 1L	[redacted]	[redacted]	[redacted]
HSCT recovery 1L	[redacted]	[redacted]	[redacted]
Post HSCT 1L maintenance	[redacted]	[redacted]	[redacted]
Health state: Relapse after HSCT 1L	[redacted]	[redacted]	[redacted]
HSCT 2L	[redacted]	[redacted]	[redacted]
HSCT recovery 2L	[redacted]	[redacted]	[redacted]
Post HSCT 2L maintenance	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained **Incremental cost per QALY gained (ICER]**	[redacted]		

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 48, and as a tornado diagram in

Figure 17. Additionally, the sensitivity analysis adjusting for additional maintenance treatment beyond trial follow-up resulted in an ICER of [redacted] DKK as incremental costs increase to [redacted] DKK (see section 11.1).

Table 48 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK]	Incremental benefit (QALYs]	ICER (DKK/QALY]
Base case	-	-	[redacted]	[redacted]	[redacted]
Relapse from CRc in the non-HSCT cohort HR: Midostaurin	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
QuizMaintenance, Mean treatment duration (cycles)	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Midostaurin-Transition probabilities (per cycle): First CR to HSCT	[redacted]	+/-20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Quizartinib-Transition probabilities (per cycle): First CR to HSCT	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Quizartinib-Transition probabilities (per cycle): Second line Relapse to Dead	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Midostaurin:Maintenance,Mean treatment duration (cycles)	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
% using treatment post-HSCT:Quizartinib	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Treatment management activities frequency (day per cycle):Hospitalisation days (cons+relapse):Relapse 2	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Quizartinib-Transition probabilities (per	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs]	ICER (DKK/QALY]
cycle): Second line CR to Second line Relapse	[redacted]		[redacted]	[redacted]	[redacted]

Figure 17 Tornado diagram

12.2.2 Probabilistic sensitivity analyses

The model parameters are varied in the model's "inputs" sheet, where the modeller can include or exclude parameters as well as vary the source of uncertainty and the distributions. Only the parameter used in the parametric extrapolations are varied in the survival parameters sheet based on their Cholesky decompositions. The mean ICER derived from the PSA was [redacted] DKK per QALY gained for quizartinib vs midostaurin. The cost effectiveness plane and the cost effectiveness acceptability curve using a hypothetical willingness to pay of [redacted] DKK are shown in Figure 16 and Figure 17. The convergence plot representing all the 1,000 iteration is shown in Figure 20

Figure 18 Cost effectiveness plane

Figure 19 Cost effectiveness acceptability curve

Figure 20 Convergence plot

12.2.3 Scenario analyses

Several scenarios were conducted testing the model base case settings (Table 49). Excluding HSCT maintenance has the highest impact on the results, limiting the incremental cost of quizartinib versus midostaurin. Excluding subsequent treatment cost increase the ICER versus the base case, limiting the benefit of quizartinib in having a longer CR. Using a cure

point of 5 years favours quizartinib, as this increases the benefits observed from having a longer CR. The use of Q-F ITT data results in small changes in the results, suggesting how the results of the economic analysis can be considered robust for the overall Q-F population.

Table 49 Scenario analysis

Scenario	Description	ICER (DKK/QALYs]	Difference from base case (%]
Base case	-	[redacted]	
Wastage not included	Wastage refers to oral treatment.	[redacted]	[redacted]
Excluding subsequent treatments drug costs	Removing gilterinib drug costs	[redacted]	[redacted]
Excluding post-HSCT maintenance for both arms	As midostaurin is not indicated after HSCT	Dominant	
Using a cure point of 5 years	5 years vs 3 in the base case	Dominant	
Naïve comparison	Efficacy based undadjusted data from Q-F<60 and RATIFY ITT population	[redacted]	[redacted]

13. Budget impact analysis

The expected number of patients treated with quizartinib matches the patients number presented in Section 3.2, assuming a 100% market share for quizartinib in the "recommendation" scenario.

Table 50 Number of new FLT3-ITD patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Quizartinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact of recommending quizartinib for the treatment of FLT3-ITD AML over 5 years is presented in Table 51. The following does not account for future Amgros discounts.

Table 51 Expected budget impact of recommending the pharmaceutical for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

For the purpose of this submission three separate interviews were held with Danish haematologists: Anne Louise Tølbøll Sørensen at Rigshospitalet Copenhagen University Hospital, Anne Stildsholt Roug and Hans Beier Ommen from Aarhus University hospital.

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Appendix A. Main characteristics of studies included

Table 52 Main characteristics of Q-F

Trial name: Q-F	NCT number: NCT02668653
Objective	The overall objective is to compare the effect of quizartinib vs. placebo (administrated with standard induction and consolidation chemotherapy, then administrated as maintenance therapy for up to 36 cycles) on OS in subjects with *FLT3*-ITD+ AML.
Publications – title, author, journal, year	Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (Q-F): a randomised, double-blind, placebo-controlled, phase 3 trial. Erba HP, Montesinos P, Kim H-J, et al. The Lancet. 2023 (10). AML-029 quizartinib prolonged overall survival (OS) vs placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients aged 18-75 years with newly diagnosed FLT3–internal tandem duplication positive (FLT3-ITD+) acute myeloid leukemia (AML]. Erba, H., Montesinos, P., Vrhovac, R., Patkowska, E., Kim, H.-J., Zak, P., Wang, P.-N., Mitov, T., Hanyok, J., & Liu, L. Clinical Lymphoma Myeloma and Leukemia. 2022 (48) S100: Quizartinib prolonged survival vs placebo plus intensive induction and consolidation therapy followed by single-agent con-tinuation in patients aged 18-75 years with newly diagnosed FLT3-ITD+ AML. Erba, H., Montesinos, P., Vrhovac, R., Patkowska, E., Kim, H.-J., Zak, P., Wang, P.-N., Mitov, T., Hanyok, J., & Liu, L. HemaSphere. 2022 (49) Quizartinib verlängert das Leben im Vergleich zu Placebo plus intensiver Induktionstherapie und Konsolidierungstherapie gefolgt von einer Behandlung mit Monotherapie bei Patienten im Alter von 18-75 Jahren mit neu diagnostizierter FLT3-ITD und AML [Abstract]. Schlenk, R., Montesinos, P., Vrhovac, R., Patkowska, E., Kim, H.-J., Zak, P., Wang, P.-N., Mi-tov, T., Hanyok, J., Liu, Benzohra, A., Lesegretain, A., Cortes, J., Perl, A., Sekeres, M., Dombret, H., Amadori, S., Wang, J., Levis, M., & Erba, H. Oncology Research and Treatment, 67. 2022 (50)
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1 ratio into two treatment arms (quizartinib or placebo). Randomisation was stratified based on region, age and WBC count. No crossover. The investigators, patients, and sponsor were masked during treatment assignment.
Sample size (n)	539 patients

Trial name: Q-F	NCT number: NCT02668653
Main inclusion criteria	1. Must be competent and able to comprehend, sign, and date an Ethics Committee or Institutional Review Board approved Informed Consent Form before performance of any study-specific procedures or tests; 2. Is ≥18 years or the minimum legal adult age (whichever is greater) and ≤75 years (at Screening); 3. Newly diagnosed, morphologically documented primary AML or AML secondary to myelodysplastic syndrome or a myeloproliferative neoplasm, based on the WHO 2008 classification (at Screening); 4. ECOG performance status 0-2 (at the time the participant signs their first approved Informed Consent Form; 5. Presence of *FLT3*-ITD activating mutation in bone marrow (allelic ratio of ≥3% *FLT3*-ITD/total *FLT3*); 6. Participant is receiving standard "7+3" induction chemotherapy regimen as specified in the protocol; 7. Adequate renal function defined as: a. Creatinine clearance >50 mL/min, as calculated with the modified Cockcroft Gault equation 8. Adequate hepatic function defined as: i) Total serum bilirubin ≤1.5 × upper limit of normal (ULN) unless the participant has documented Gilbert's syndrome or the increase is related to increased unconjugated (indirect) bilirubin due to hemolysis; ii) Serum alkaline phosphatase, aspartate transaminase and alanine transaminase ≤2.5 × ULN; 9. Serum electrolytes within normal limits: potassium, calcium (total, or corrected for serum albumin in case of hypoalbuminemia or ionized calcium) and magnesium. If outside of normal limits, participant will be eligible when electrolytes are corrected; 10. If a woman of childbearing potential, must have a negative serum pregnancy test upon entry into this study and must be willing to use highly effective birth control upon enrollment, during the treatment period and for 6 months following the last dose of investigational drug or cytarabine, whichever is later. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months); 11. If male, must be surgically sterile or willing to use highly effective birth control upon enrollment, during the treatment period, and for 6 months following the last dose of investigational drug or cytarabine, whichever is later.
Main exclusion criteria	1. Diagnosis of acute promyelocytic leukaemia (APL), French-American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or breakpoint cluster region-Abelson murine leukaemia viral oncogene homolog 1 positive leukaemia (ie, chronic myelogenous leukaemia in blast crisis); participants who undergo diagnostic workup for APL and treatment with all-trans retinoic acid, but who are found not to have APL, are eligible (treatment with all-trans retinoic acid must be discontinued before starting induction chemotherapy).

2. Diagnosis of AML secondary to prior chemotherapy or radiotherapy for other neoplasms;
3. Prior treatment for AML, except for the following allowances:
    - Leukapheresis;
    - Treatment for hyperleukocytosis with hydroxyurea;
    - Cranial radiotherapy for central nervous system (CNS) leukostasis;
    - Prophylactic intrathecal chemotherapy;
    - Growth factor/cytokine support;
4. Prior treatment with quizartinib or other *FLT3*-ITD inhibitors;
5. Prior treatment with any investigational drug or device within 30 days prior to randomisation (within 2 weeks for investigational or approved immunotherapy) or currently participating in other investigational procedures;
6. History of known CNS leukaemia, including cerebrospinal fluid positive for AML blasts; lumbar puncture is recommended for participants with symptoms of CNS leukaemia to rule out extramedullary CNS involvement;
7. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumours curatively treated with no evidence of disease for at least 2 years;
8. Uncontrolled or significant cardiovascular disease, including any of the following:
    - Bradycardia of less than 50 beats per minute, unless the participant has a pacemaker;
    - Fridericia's Heart Rate Correction Formula (QTcF) interval >450 msec;
    - Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome);
    - Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg;
    - History of clinically relevant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes);
    - History of second (Mobitz II) or third degree heart block (participants with pacemakers are eligible if they have no history of fainting or clinically relevant arrhythmias while using the pacemaker);
    - History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to Screening;
    - History of New York Heart Association Class 3 or 4 heart failure;
    - Known history of left ventricular ejection fraction ≤45% or less than the institutional lower limit of normal;
    - Complete left bundle branch block;
9. Active acute or chronic systemic fungal, bacterial, or viral infection not well controlled by antifungal, antibacterial or antiviral therapy;

Trial name: Q-F	NCT number: NCT02668653
	10. Known active clinically relevant liver disease (e.g., active hepatitis B, or active hepatitis C); 11. Known history of human immunodeficiency virus. Participants should be tested for human immunodeficiency virus prior to randomisation if required by local regulations or Ethics Committee; 12. History of hypersensitivity to any excipients in the quizartinib/placebo tablets; 13. Females who are pregnant or breastfeeding; 14. Otherwise considered inappropriate for the study by the Investigator.
Intervention	268 patients received quizartinib. <u>Induction</u> Cycle 1, 28-days: 35.4 mg (2 × 17.7 mg) quizartinib orally once daily on days 8-21 of 7 + 3 (cytarabine [100 or 200 mg/m^2/day) IV on days 1 through 8 + daunorubicin [60 mg/m^2/day) IV or idarubicin [12 mg/m^2/day) IV on days 1-3). Cycle 2, 28-days: 35.4 mg (2 × 17.7 mg) quizartinib orally once daily on days 8-21 or days 6-19 of an optional second induction (7 + 3 or 5 + 2 [5 days cytarabine IV + 2 days daunorubicin IV or idarubicin IV)). <u>Consolidation</u> 35.4 mg quizartinib orally once daily on days 6 to 19 of high-dose cytarabine (1.5-3 g/m^2 every 12 hours on days 1, 3, and 5) for up to four 28-day cycles and/or HSCT. • Cytarabine among subjects <60 years old: 3.0 g/m^2 IV infusion, every 12 hours. • Cytarabine among subjects ≥60 years old: 1.5 g/m^2 IV infusion, every 12 hours <u>Maintenance:</u> • Starting dose of 26.5 mg quizartinib once daily for two weeks if QTcF is ≤ 450 ms. • After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg (2 × 26.5 mg) once daily. • Single-agent maintenance therapy may be continued for up to thirty-six 28-day cycles.
Comparator	271 patients received the placebo. <u>Induction</u> Cycle 1, 28-days: 35.4 mg (2 × 17.7 mg) placebo orally once daily on days 8-21 of 7 + 3. Cycle 2, 28-days: 35.4 mg (2 × 17.7 mg) placebo orally once daily on days 8-21 or days 6-19 of an optional second induction of 7 + 3 or 5 + 2. <u>Consolidation</u> 35.4 mg placebo orally once daily on days 6 to 19 of high-dose cytarabine (1.5-3 g/m^2 every 12 hours on days 1, 3, and 5) for up to four 28-day cycles and/or HSCT. <u>Maintenance:</u> • Starting dose of 26.5 mg placebo once daily for two weeks if QTcF is ≤ 450 ms.

Trial name: Q-F	NCT number: NCT02668653
	• After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg (2 × 26.5 mg) once daily. • Single-agent maintenance therapy may be continued for up to thirty-six 28-day cycles.
Follow-up time	Median follow-up of 39.2 months (range quizartinib: 32.2-45.4. range placebo: 31.4-46.0)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was OS in subjects with newly diagnosed AML with *FLT3*-ITD. Secondary endpoints were EFS, CRc rate after induction, percentage of subjects achieving CRc with *FLT3*-ITD MRD negativity after induction, CR rate after induction, and percentage of subjects achieving CR with *FLT3*-ITD MRD negativity after induction. Exploratory endpoints included RFS, duration of CR, CR rate at the end of first induction cycle, CRc rate at the end of first induction cycle and transplantation rate, change in EQ-5D-5L **Other endpoints:** Rate of CR with partial hematologic recovery after induction (only for IRC assessment of response), rate of morphologic leukaemia-free state after induction (only for IRC assessment of response), RFS in subjects who entered the continuation phase after achieving CRc in induction, healthcare resource utilisation and change in EORTC and QLQ-C30 were included as exploratory endpoints but not included in this application.
Method of analysis	All efficacy analyses were ITT analyses. Median OS and EFS was calculated based on KM method. HR with 95% CI was estimated with a stratified Cox regression analysis.
Subgroup analyses	Subgroup analyses for OS and EFS were conducted for the following prespecified subgroups: • Age: <60 years, ≥60 years to <65 years, ≥65 year • Sex: male, female • Race: White, Black or African American, Asian, other defined in electronic case report form • Region: North America, Europe, Asia/other regions • WBC count at the time of diagnosis of AML: <40x10^9/L, ≥40x10^9/L • Choice of anthracycline: daunorubicin, idarubicin • AML cytogenetic risk score: favourable, intermediate, unfavourable, unknown • By baseline ECOG performance status: 0, 1, 2 • *FLT3-ITD* variant allelic frequency (using central testing) at randomisation: <3%, ≥3% to ≤25%, >25% to ≤50%, >50% • NPM1 mutational status: yes, no • Concomitant use of strong CYP3A4 inhibitor: yes, no (for ECG analyses only)

Trial name: Q-F	NCT number: NCT02668653
	• Concomitant use of QT-prolonging medications in The Arizona Center for Education and Research on Therapeutics (AZCERT) classification "known risk": yes, no (for ECG analyses only) The analyses were conducted similarly to the primary analysis of OS, except the analyses were performed without stratification, and p-values were not reported. When the total number of subjects in any subgroup category was fewer than 30, no analysis for that category was performed, and only the number of subjects and number of events for each treatment in that category were summarised. If the total number of subjects in any subgroup category was fewer than 5, no summary for that category was provided. Treatment-emergent adverse events and notable ECG results by age, sex, race, and choice of anthracycline subgroups were summarised descriptively. For notable ECG results, summaries of additional subgroups (concomitant use of strong CYP3A4 inhibitor [yes, no] and concomitant use of QT-prolonging medications in AZCERT classification "known risk" [yes, no]) were also provided.
Other relevant information	N/A

Source: ClinicalTrials.gov, 2016 (46); Daiichi Sankyo, Inc., 2022 (8); Daiichi Sankyo, Inc., 2023(33); Erba et al., 2023 (10).

Table 53 Main characteristics of RATIFY

Trial name: RATIFY	NCT number: NCT00651261
Objective	The overall objective of the study is to determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and maintenance therapy improves OS in both the mutant *FLT3*-ITD and *FLT3*-TKD AML patients.
Publications – title, author, journal, year	Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation, Stone et al., The new England Journal of Medicine, 2017 (2). Molecular landscape and prognostic impact of FLT3-ITD insertion site in acute myeloid leukemia: RATIFY study results. Rücker FG, et al. Leukemia. 2022 (3). Midostaurin in patients with acute myeloid leukemia and FLT3-TKD mutations: a subanalysis from the RATIFY trial, Voso et al., Blood advances, 2020 (51). Impact of NPM1/FLT3-ITD genotypes defined by the 2017 European LeukemiaNet in patients with acute myeloid leukemia. Dohner, H. et al. Blood Adv. 2020 (52). European Medicines Agency review of midostau-rin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis. Tzogani, K. et al. ESMO Open.2019 (53). Midostaurin reduces relapse in FLT3-mutant acute myeloid leukemia: the Alliance CALGB 10603/RATIFY trial. Larson, R. A., et al. Leukemia.2021 (54).
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1 ratio into two treatment groups (midostaurin or placebo). Randomisation was stratified based on the subtype of *FLT3* mutation: TKD, or ITD with either a high ratio (>0.7) or

Trial name: RATIFY	NCT number: NCT00651261
	a low ratio (0.05 to 0.7) of mutant to wild-type alleles (ITD [high] and ITD [low], respectively). No crossover. The investigators and patients were masked during treatment assignment.
Sample size (n)	717 patients
Main inclusion criteria	1. Documentation of disease: ○ Unequivocal diagnosis of AML (> 20% blasts in the bone marrow based on the WHO classification), excluding M3 (acute promyelocytic leukemia). Patients with neurologic symptoms suggestive of CNS leukaemia are recommended to have a lumbar puncture. Patients whose cerebrospinal fluid is positive for AML blasts are not eligible. ○ Documented *FLT3* mutation (ITD or point mutation), determined by analysis in a protocol-designated *FLT3* screening laboratory. 2. Age requirement: ○ Age ≥ 18 and < 60 years 3. Prior therapy: ○ No prior chemotherapy for leukaemia or myelodysplasia with the following exceptions: ▪ emergency leukapheresis ▪ emergency treatment for hyperleukocytosis with hydroxyurea for ≤ 5 days ▪ cranial radiation therapy for CNS leukostasis (one dose only) ▪ growth factor/cytokine support ○ AML patients with a history of antecedent myelodysplasia remain eligible for treatment on this trial, but must not have had prior cytotoxic therapy (e.g., azacitidine or decitabine) ○ Patients who have developed therapy related AML after prior radiation therapy or chemotherapy for another cancer or disorder are not eligible. 4. Cardiac function: Patients with symptomatic congestive heart failure are not eligible. 5. Initial Laboratory Value: Total bilirubin < 2.5 x ULN 6. Pregnancy and nursing status: ○ Non-pregnant and non-nursing due to the unknown teratogenic potential of midostaurin in humans, pregnant or nursing patients may not be enrolled. ○ Women of childbearing potential must have a negative serum or urine pregnancy test within a sensitivity of at least 50 mIU/mL within 16 days prior to registration. ○ Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or commit to two acceptable methods of birth control: ▪ one highly effective method (e.g., intrauterine device, hormonal (non-oral

Trial name: RATIFY	NCT number: NCT00651261
	contraceptive, tubal ligation, or partner's vasectomy) and ▪ one additional effective method (e.g., latex condom, diaphragm, or cervical cap) ○ The two acceptable methods of birth control must be used at the same time, before beginning midostaurin/placebo therapy and continuing for 12 weeks after completion of all therapy. ○ Note that oral contraceptives are not considered a high effective method because of the possibility of a drug interaction with midostaurin. ○ Women of childbearing potential is defined as a sexually active mature woman who has not undergone a hysterectomy or who has not had menses at any time in the preceding 24 consecutive months. ○ Men must agree not to father a child and must use a latex condom during any sexual contact with women of childbearing potential while taking midostaurin/placebo and for 12 weeks after therapy is stopped, even if they have undergone a successful vasectomy.
Main exclusion criteria	N/A, see above "Main inclusion criteria".
Intervention	360 patients received midostaurin. Induction: 50 mg midostaurin orally twice daily on days 8-21 of daunorubicin 60 mg/m^2 IV on days 1-3 and cytarabine 200 mg/m^2 IV on days 1-7. Consolidation: Patients achieving complete remission received four 28-day cycles of high dose cytarabine (3000 mg/m^2) administered over a period of 3 hours every 12 hours on days 1, 3, and 5 and midostuarin 50 mg orally twice daily on days 8-21. Maintenance: Patients who remained in remission after completion of consolidation therapy entered a maintenance phase in which they received midostaurin 50 mg orally twice daily for twelve 28-day cycles.
Comparator	357 patients received the placebo. Induction: 50 mg placebo orally twice daily on days 8-21 of daunorubicin 60 mg/m^2 IV on days 1-3 and cytarabine 200 mg/m^2 IV on days 1-7. Consolidation: Four 28-day cycles of high dose cytarabine (3000 mg/m^2) administered over a period of 3 hours every 12 hours on days 1, 3, and 5 and placebo 50 mg orally twice daily on days 8-21. Maintenance: Placebo 50 mg orally twice daily for twelve 28-day cycles.
Follow-up time	Median follow-up was 59 months.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was OS. Secondary endpoints were EFS and CR rate. **Other endpoints:**

Trial name: RATIFY	NCT number: NCT00651261
	OS censoring participants who receive a stem cell transplant at the time of the transplant, DFS, and DFS rate one year after completing the planned maintenance phase were included as secondary endpoints in the study, but results are not included in this application.
Method of analysis	All efficacy analyses were ITT analyses. The median OS and EFS with 95% CI was estimated using the KM method.
Subgroup analyses	Subgroup analysis according to *FLT3* subtype in the ITT population. KM method and HR. The trial was not powered for subgroup analyses.
Other relevant information	Midostaurin inhibits multiple receptor tyrosine kinases, including *FLT3* and KIT kinase. *In vitro* data indicate that midostaurin inhibits D816V mutant KIT receptors at exposure levels achieved in patients (average achieved exposure higher than IC_{50}). *In vitro* data indicate that KIT wild type receptors are inhibited to a much lesser extent at these concentrations (average achieved exposure lower than IC_{50}). Midostaurin interferes with aberrant KIT D816V-mediated signalling and inhibits mast cell proliferation, survival, and histamine release.

Source: ClinicalTrials.gov, 2008 (9); Stone et al., 2017 (2); European Medicines Agency, 2017 (43).

Appendix B. Efficacy results per study

Results per study

Table 54 Results per Q-F < 60

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS (13 Aug 2021)	Quizartinib	161	NE (NE–NE)	N/A	N/A	N/A	HR: 0.684	0.493–0.949	[redacted]	Median OS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	(63)
	Placebo	162	23.0 (13–NE)								
6 months OS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
12 months OS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
24 months OS rate	Placebo	162	[redacted]								
36 months OS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
48 months OS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
Median EFS (13 Aug 2021)	Quizartinib	161	0.0 (0.0–7.6)	N/A	N/A	N/A	HR: 0.859	0.662–1.115	[redacted]	Median EFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	(63)
	Placebo	162	0.5 (0.0–5.1)								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
6 months EFS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
12 months EFS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
18 months EFS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
24 months EFS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
30 months EFS rate	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	162	[redacted]								
	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
36 months EFS rate	Placebo	162	[redacted]								
CR (13 Aug 2021)	Quizartinib	161	55.9%, (47.9, 63.7)	N/A	N/A	N/A	N/A	N/A	N/A	95% CI is based in the Clopper-Pearson method for single proportion.	(62)
	Placebo	162	55.6%, (47.6, 63.4)								
Median CR in months (13 Aug 2021)	Quizartinib	161	[redacted]	N/A	N/A	N/A	HR: [redacted]	[redacted]	[redacted]	Median CR is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	(62)
	Placebo	162	[redacted]								
CRi rate (13 Aug 2021)	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(63)
	Placebo	162	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median CRi in months (13 Aug 2021)	Quizartinib	161	[redacted]	N/A	N/A	N/A	HR: [redacted]	[redacted]	[redacted]	Median CRi is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	(63)
	Placebo	162	[redacted]								
CRc rate (13 Aug 2021)	Quizartinib	161	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	95% CI is based in the Clopper-Pearson method for single proportion.	(62)
	Placebo	162	[redacted]								
Median CRc in months (13 Aug 2021)	Quizartinib	161	[redacted]	N/A	N/A	N/A	HR: [redacted]	[redacted]	[redacted]	Median CRc is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided	(62)
	Placebo	162	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										p-value from unstratified log-rank test.	
CIR (13 Aug 2021)	Quizartinib	90	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(64)
	Placebo	90	[redacted]								
12 months CIR rate	Quizartinib	90	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(64)
	Placebo	90	[redacted]								
24 months CIR rate	Quizartinib	90	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(64)
	Placebo	90	[redacted]								
36 months CIR rate	Quizartinib	90	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(64)
	Placebo	90	[redacted]								
Median RFS (subjects in CRc) (13 Aug 2021)	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	HR: [redacted]	[redacted]	[redacted]	Median RFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided	(63)
	Placebo	[redacted]	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										p-value from unstratified log-rank test.	
6 months RFS (subjects in CRc) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	[redacted]	[redacted]								
12 months RFS (subjects in CRc) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	[redacted]	[redacted]								
24 months RFS (subjects in CRc) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	[redacted]	[redacted]								
36 months RFS (subjects in CRc) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	[redacted]	[redacted]								
48 months RFS (subjects	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	[redacted]	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
in CRc) rate											
Median RFS (subjects in CR) (13 Aug 2021)	Quizartinib	90	NE (NE, NE)	N/A	N/A	N/A	HR: 0.425	0.263, 0.687	[redacted]	Median RFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	(62)
	Placebo	90	17.2 (10.5, NE)								
6 months RFS (subjects in CR) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(62)
	Placebo	[redacted]	[redacted]								
12 months RFS (subjects in CR) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(62)
	Placebo	[redacted]	[redacted]								
18 months	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(62)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
RFS (subjects in CR) rate	Placebo	[redacted]	[redacted]								
24 months RFS (subjects in CR) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(62)
	Placebo	[redacted]	[redacted]								
30 months RFS (subjects in CR) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(62)
	Placebo	[redacted]	[redacted]								
36 months RFS (subjects in CR) rate	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(62)
	Placebo	[redacted]	[redacted]								
Median DUR (13 Aug 2021)	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	HR: [redacted]	[redacted]	[redacted]	Median DUR is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model with treatment as	(63)
	Placebo	[redacted]	[redacted]								

Results of Q-F (NCT02668653)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	
KM estimated DUR at 6 months	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(63)
	Placebo	[redacted]	[redacted]								
KM estimated DUR at 12 months	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(63)
	Placebo	[redacted]	[redacted]								
KM estimated DUR at 24 months	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(63)
	Placebo	[redacted]	[redacted]								
KM estimated DUR at 36 months	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(63)
	Placebo	[redacted]	[redacted]								
KM estimated DUR at	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(63)
	Placebo	[redacted]	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
48 months											
Protocol-specified HSCT (13 Aug 2021)	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens). CI is based on the Clopper-Pearson method.	(63)
	Placebo	[redacted]	[redacted]								
Non-protocol-specified HSCT (13 Aug 2021)	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Any HSCT performed for other reasons, e.g. molecular relapse, will be considered non-protocol-specified AML therapy, and the subject will be discontinued from quizartinib or placebo but will continue to be followed for outcome data.	(63)
	Placebo	[redacted]	[redacted]								
Median time to discontinuation (13 Aug 2021)	Quizartinib	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	Median time to discontinuation is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR is from unstratified Cox proportional hazards model	(61)
	Placebo	[redacted]	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										with treatment as the only categorical variable in the model. Confidence limits are based on the Wald test. Two-sided p-value from unstratified log-rank test.	

Sources: Daiichi Sankyo Inc., 2023 (63); Daiichi Sankyo Inc., 2023 (61); Daiichi Sankyo Inc., 2023 (62); Daiichi Sankyo Inc., 2022 (64).

Table 55 Results per Q-F ITT population

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS (13 Aug 2021)	Quizartinib	268	31.9 months (21.0-NE)	16.8	N/A	N/A	HR: 0.78	0.62–0.98	0.032	Median OS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR with 95% CI was estimated with a stratified Cox regression analysis.	(8)
	Placebo	271	15.1 months (13.2-26.2)								
	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
6 months OS rate	Placebo	271	[redacted]								
12 months OS rate	Quizartinib	268	67.4% (61.3-72.7)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	57.7% (51.6-63.4)								
24 months OS rate	Quizartinib	268	54.7% (48.4-60.5)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	44.7% (38.7-50.6)								
36 months OS rate	Quizartinib	268	49.9% (43.7-55.9)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	41.1% (35.0-47.0)								
48 months OS rate	Quizartinib	268	48.4% (41.9-54.5)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	37.0% (29.8-44.2)								
Median EFS (13 Aug 2021)	Quizartinib	268	0.03 months (0.03-0.95)	N/A	N/A	N/A	HR: 0.92	0.75-1.11	0.2371	Median EFS is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method. HR with	(8)
	Placebo	271	0.71 months (0.03-3.42)								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										95% CI was estimated with a stratified Cox regression analysis.	
6 months EFS rate	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	[redacted]								
12 months EFS rate	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	[redacted]								
18 months EFS rate	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	[redacted]								
24 months EFS rate	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
30 months EFS rate	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	[redacted]								
36 months EFS rate	Quizartinib	268	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the Kaplan-Meier method.	(8)
	Placebo	271	[redacted]								
CR (13 Aug 2021)	Quizartinib	268	147 (54.9%), (48.7-60.9)	3 (0.5%)	N/A	[redacted]	N/A	N/A	N/A	95% CI is based in the Clopper-Pearson method. The p-value is based on the Cochran-Mantel-Haenszel test adjusted for stratification factors[a]. P-value is 2-sided.	(8)
	Placebo	271	150 (55.4%), (49.2-61.4)								
CRc rate (13 Aug 2021)	Quizartinib	268	192 (71.6%) (65.8-77.0)	3 (6.7%)	N/A	[redacted]	N/A	N/A	N/A	95% CI is based in the Clopper-Pearson method. The p-value is based on the Cochran-Mantel-Haenszel test adjusted for stratification factors[a]. P-value is 2-sided.	(8)
	Placebo	271	176 (64.9%) (58.9-70.6)								
	Quizartinib	268	45 (16.8%), (12.5-21.8)	N/A	N/A	[redacted]	N/A	N/A	N/A	95% CI is based in the Clopper-Pearson method.	(8)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CRi[b] (13 Aug 2021)	Placebo	271	26 (9.6%), (6.4-13.7)							The p-value is based on the Cochran-Mantel-Haenszel test adjusted for stratification factors[a]. P-value is 2-sided.	
CIR (13 Aug 2021)	Quizartinib	142	44 (29.9%)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(8)
	Placebo	150	63 (42.0%)								
12 months CIR rate	Quizartinib	142	18.7 (12.7-25.6)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(8)
	Placebo	150	34.9 (27.1-42.7)								
24 months CIR rate	Quizartinib	142	31.2 (23.5-39.2)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(8)
	Placebo	150	43.3 (34.9-51.3)								
36 months CIR rate	Quizartinib	142	33.8 (25.5-42.2)	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the cumulative incidence function.	(8)
	Placebo	150	45.1 (36.5-53.2)								
Median RFS	Quizartinib	192	28.5 months (18.5-NE)	N/A	N/A	N/A	HR: 0.733	0.554, 0.969	N/A	Median RFS is from KM analysis. CI for median is	(8)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
(subjects in CRc[c]) (13 Aug 2021)	Placebo	176	12.6 months (9.7-23.7)							computed using the Brookmeyer-Crowley method. The HR is based on an unstratified Cox regression analysis.	
6 months RFS (subjects in CRc[c]) rate	Quizartinib	192	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	176	[redacted]								
12 months RFS (subjects in CRc[c]) rate	Quizartinib	192	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	176	[redacted]								
18 months RFS (subjects in CRc[c]) rate	Quizartinib	192	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	176	[redacted]								
24 months	Quizartinib	192	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
RFS (subjects in CRc[c]) rate	Placebo	176	[redacted]								
30 months RFS (subjects in CRc[c]) rate	Quizartinib	192	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	176	[redacted]								
36 months RFS (subjects in CRc[c]) rate	Quizartinib	192	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	176	[redacted]								
Median RFS (subjects in CR[d]) (13 Aug 2021)	Quizartinib	147	39.3 months (22.6-NE)	N/A	N/A	N/A	HR: 0.613	0.444-0.845	N/A	Median RFS is from KM analysis. CI for median is computed using the Brookmeyer-Crowley method. The HR is based on unstratified Cox regression analysis.	(8)
	Placebo	150	13.6 months (9.7-23.7)								
6 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
RFS (subjects in CR[d]) rate	Placebo	150	[redacted]								
12 months RFS (subjects in CR[d]) rate	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
18 months RFS (subjects in CR[d]) rate	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
24 months RFS (subjects in CR[d]) rate	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
30 months RFS (subjects	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
in CR[d]) rate											
36 months RFS (subjects in CR[d]) rate	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
Median duration of CR (13 Aug 2021)	Quizartinib	147	38.6 (21.9-NE)	N/A	N/A	N/A	HR: 0.621	0.451-0.857	N/A	Median duration of CR is from Kaplan-Meier analysis. CI for median is computed using the Brookmeyer-Crowley method.	(8)
	Placebo	150	12.4 (8.8-22.7)								
KM estimated duration of CR at 6 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
KM estimated duration of CR at 12 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
KM estimated duration of CR at 18 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
KM estimated duration of CR at 24 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
KM estimated duration of CR at 30 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
KM estimated duration of CR at 36 months	Quizartinib	147	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated using the KM method.	(8)
	Placebo	150	[redacted]								
Protocol-	Quizartinib	268	102 (38.1%) (32.2-44.2)	N/A	N/A	N/A	N/A	N/A	N/A	Subjects with protocol-specified HSCT are	(8)

Results of Q-F (NCT02668653)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
specified HSCT (13 Aug 2021)	Placebo	271	91 (33.6%) (28.0-39.5)							subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens).	
Protocol-specified HSCT and non-protocol-specified HSCT (13 Aug 2021)	Quizartinib	268	144 (53.7%)	N/A	N/A	N/A	N/A	N/A	N/A	Any HSCT performed for other reasons, e.g. molecular relapse, will be considered non-protocol-specified AML therapy, and the subject will be discontinued from quizartinib or placebo but will continue to be followed for outcome data.	(8)
	Placebo	271	128 (47.2%)								

Notes: [a] Stratification factors adjusted for include region (North America, Europe, Asia/Other Regions), age (<60, ≥60 years old), and White blood cell count at the time of diagnosis of AML (<40x109/L, ≥40x109/L). [b] CRi was not specified as a secondary endpoint but is included for completeness. Based on assessments by the end of induction. [c] RFS for subjects achieving CRc in induction. d RFS for subjects achieving CR in induction.
Source: Daiichi Sankyo Inc, 2022, table 8.1, table 8.4, table 8.7, table 14.2.3, table 8.10, table 14.2.4.1, table 14.2.5, table 14.2.6, table 14.2.1.2 (8).

Table 56 Results per RATIFY

Results of RATIFY (NCT00651261)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS (7 March 2016)	Midostaurin	360	74.7 months (31.5–NE)	49.1	N/A	N/A	HR: 0.78	0.63–0.96	0.009	The median survival is based on the KM estimator. The p-value is one-sided by stratified log-rank test.	Stone et al. 2017 (2)
	Placebo	357	25.6 months (18.6-42.9)								
4-year OS rate	Midostaurin	360	51.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Stone et al. 2017 (2)
	Placebo	357	44.3								
Median EFS (7 March 2016)	Midostaurin	360	8.2 (5.4-10.7) months	5.2	N/A	0.002	HR: 0.78	0.66–0.93	0.002	The median EFS with 95% CI was estimated using the Kaplan-Meier method. The p-value for the absolute difference is one-sided by stratified log-rank test. The p-value for the relative difference is one-sided by stratified score test.	Stone et al. 2017 (2) Clinicaltrials.gov, 2008 (9)
	Placebo	357	3.0 (1.9-5.9) months								
4-year EFS rate	Midostaurin	360	28.2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Stone et al. 2017 (2)
	Placebo	357	20.6								
Protocol-	Midostaurin	360	212 (58.9%) (53.6-64.0)	21 (5.4%)	N/A	0.15	N/A	N/A	N/A		Stone et al. 2017 (2)

Results of RATIFY (NCT00651261)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
specified CR rate (7 March 2016)	Placebo	357	191 (53.5%) (48.2-58.8)							P value is two-sided and was calculated with the use of Fisher's exact test.	
Median time to CR (7 March 2016)	Midostaurin	360	35 days (20-60)	N/A	N/A	N/A	N/A	N/A	N/A	Based on KM estimate.	Stone et al. 2017 (2)
	Placebo	357	35 days (20-60)								
Median CIR (7 March 2016)	Midostaurin	212	NE (NE-31.3)	N/A	N/A	N/A	N/A	N/A	N/A	A competing risks analysis with death from any cause as a competing risk, was used to compute the cumulative incidence curves for relapse among patients achieving a CR and compared between the arms. A competing risk analysis was conducted as death prevents the occurrence of relapse, which in this case is the primary event of interest.	Stone et al. 2017 (2)
	Placebo	191	NE (NE-17.6)								

Source: Stone et al. 2017 (2); Clinicaltrials.gov, 2008 (9).

Appendix C. Comparative analysis of efficacy

C.1 Methodology

Determination of treatment effect modifiers

Literature review for potential TEMs in RATIFY

Subgroup analyses presented in the publications of the RATIFY trial were evaluated for the reporting of clinical subgroups across which the treatment effect varied. RATIFY subgroup analyses were only available for the OS outcome and included an assessment of sex, age, *FLT3* subtype, ELN risk, *NPM1* mutation status, and WBC count. Out of the analysed selection, age, *NPM1* mutation status and ELN risk had shown statistically significant results in the subgroup analyses and thus were considered potential TEMs. These results should be interpreted with caution however, as the sample size was small for the majority of subgroups. No potential TEMs were identified for CR and CIR from the RATIFY literature (10, 81) as RATIFY *FLT3*-ITD+ subgroup analyses were reported for OS only.

Quantitative assessment for TEMs in Q-F

While only aggregated data is available for RATIFY, IPD from Q-F was leveraged to conduct interaction analyses to assess the potential treatment-modifying effect of baseline characteristics. A prognostic variable test was completed to identify any baseline characteristics which may influence the outcomes of interest and a univariate regression analysis was then conducted utilising Q-F IPD to identify TEMs (i.e. characteristics affecting the treatment effect of quizartinib added to chemotherapy vs. chemotherapy alone) by introducing interaction terms of baseline characteristics with treatment in a regression model. Variables showing statistically significant association with treatment at the 75% significance level ($p \leq 0.25$) for the effect modifier test and not containing a large number of missing values, were flagged for subsequent clinical consideration (Table 57). *FLT3-ITD*$_{low}$ vs. *FLT3-ITD*$_{high}$ status, cytogenetic risk and bone marrow blast count was identified as potential TEMs for OS in Q-F. Specifically, a better treatment effect was exhibited in patients with *FLT3-ITD*$_{high}$ risk compared to those with *FLT3-ITD*$_{low}$ risk. A better treatment effect was also demonstrated in patients with a higher level of bone marrow blasts. Similar trends were demonstrated in patients with intermediate, adverse, and unknown cytogenetic risk compared to those with low cytogenetic risk (7).

Table 57. Interaction analysis in Q-F on covariate association with OS and treatment effect modifying status

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

Notes: Analysis results are shown for the Q-F ITT population.
Source: Daiichi Sankyo Inc., 2023 (7).

Expert consultation

In line with TSD 18 (65), three clinical experts were consulted to determine whether all relevant TEMs had been identified and to rank them according to importance. Clinicians indicated that the TEMs identified from the literature and the interaction analysis of Q-F data were plausible. From a clinical perspective, age, sex, *FLT3* mutation status, platelet count, *NPM1* mutation status, and bone marrow blasts were considered TEMs for the outcomes of interest. Bone marrow blasts scored relatively low on the importance scale and thus it was not used as a TEM in the MAIC which was limited by the ESS (Table 58). Cytogenetic risk, WBC count, ANC, race, and geographical region of patients were flagged as potential TEMs, with the former two considered most impactful. However, due to an absence of comparable data it was not possible to re-weight the population of Q-F and the *FLT3-ITD*+ population of RATIFY according to these TEMs (7).

Table 58. Overview of TEM variables by derivation technique and inclusion in base case analysis (ITD+)

TEM	Method for identification	Considered for base case

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

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Notes: [a] this TEM was later excluded from the base case as it resulted in an ESS that was less than 50% of the original sample size. It was included as a TEM in the scenario analysis. [b] These were not included as they were judged to be low in terms of importance during expert consultation. [c] Expert consultation/interaction analysis identified these as TEMs. However, they were not reported in the Rücker et al. publication (3)publication (3), and thus matching could not be performed on these variables.
Source: Daiichi Sankyo Inc., 2023 (7).

MAIC calculations

Propensity score weights were estimated using logistic regression:

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

Where X_{it}^{EM} is the effect modifier covariate vector for the *i*-th individual in Q-F study and w_{it} is the weight of the *i*-th individual.
The ESS was estimated as:

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

ESS is defined as 'the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate' (65). A small ESS is indicative of highly variable weights due to a lack of population overlap and as such, the estimates may be unstable. ESS is defined as 'the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate' (65). A small ESS is indicative of highly variable weights due to a lack of population overlap and as such, the estimates may be unstable.
Rescaled weights were calculated using the following formula:

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

where N is the number of subjects in Q-F. Rescaled weights > 1 indicate that a patient carries more weight in the reweighted pseudo-population than the original trial sample,

while a rescaled weight <1 means that an individual carries less weight in the reweighted population than the original data (7).

Relative treatment effects for outcomes (OS, CR and CIR) were estimated using log HR and OR and their standard errors. The choice of log HR/OR – the linear predictor – scale follows the NICE MAIC recommendations (65). The assumed linearity, additivity of treatment effects and treatment effect modification on this scale is required for estimating the relative treatment effect of quizartinib and midostaurin in the target (AC) population. The choice of log HR/OR – the linear predictor – scale follows the NICE MAIC recommendations (65). The assumed linearity, additivity of treatment effects and treatment effect modification on this scale is required for estimating the relative treatment effect of quizartinib and midostaurin in the target (AC) population:

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

where A is placebo, B is quizartinib, C is midostaurin, g is a link function – log(.) in this case, $\hat{\Delta}_{BC(AC)}$ is the (indirect) relative treatment effect (HR) of quizartinib vs. midostaurin in the target AC population, $\hat{\Delta}_{AC(AC)}$ is the treatment effect (HR) of placebo vs. midostaurin in the target AC population and $\hat{\Delta}_{AB(AC)}$ is the treatment effect (HR) of placebo vs. quizartinib - estimated using MAIC reweighting and applying the weighted Cox proportional hazards (PH) model - in the target AC population (2).

The bootstrap was performed using 1,000 bootstrap samples, and the 95% CI was estimated using the 2.5th and 97.5th percentiles of the bootstrap distributions.

C.2 Results

Overall survival

The HR pre and post matching are reported in Table 59. Matching shifted upwards the quizartinib OS KM curves, as indicated by the resulting HR and as shown in Figure 21. OS endpoints for both Q-F and RATIFY are presented in sections 6.1.4.1 and 6.1.5.1, respectively.

Table 59 Summary of OS HR (Q-F ≤60 and RATIFY FLT3-ITD+ populations)

Data	Comparison	HR (95% CI)
Q-F unadjusted	Quizartinib vs placebo	0.68 (0.50, 0.94)
Q-F adjusted	Quizartinib vs placebo	0.65 (0.42, 1.00)
RATIFY	Midostaurin vs placebo	0.79 (0.59, 1.06)
Naïve	Quizartinib vs Midostaurin	0.87 (0.56, 1.34)
MAIC	Quizartinib vs Midostaurin	0.82 (0.48, 1.39)

Source: Daiichi Sankyo, 2023 (7).

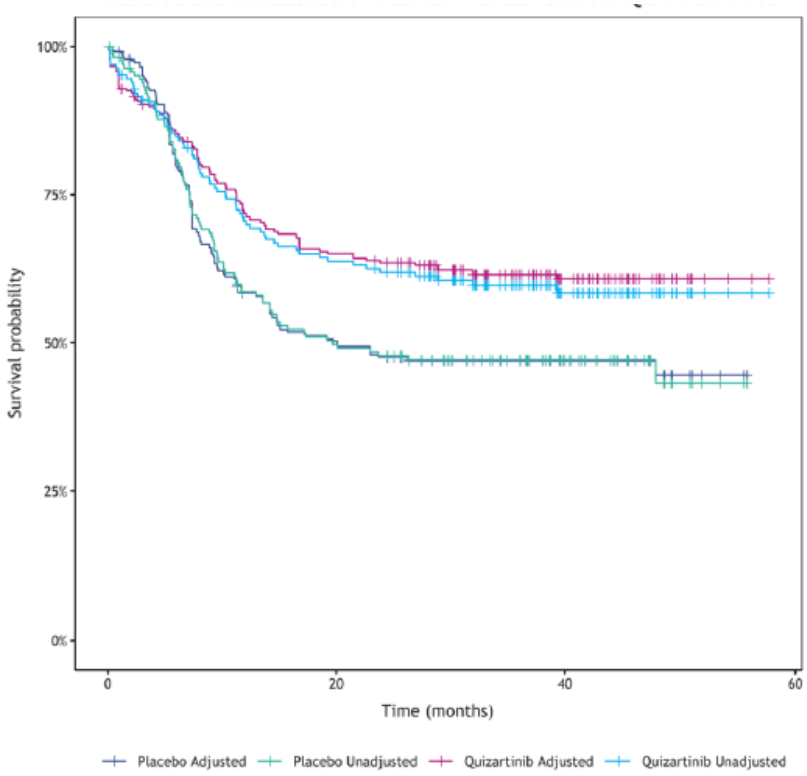

Figure 21 Matched and unmatched Q-F ≤ 60 years old OS (with RATIFY ITD+)

Complete Remission

The OR pre and post matching are reported in Table 60. CR endpoints for both Q-F and RATIFY are presented in sections 0 and 6.1.5.3, respectively.

Table 60 Summary of CR OR (Q-F ≤60 y.o and RATIFY FLT3-ITD+ populations)

Data	Comparison	OR (95% CI)
Q-F unadjusted	Quizartinib vs placebo	1.04 (0.67, 1.60)
Q-F adjusted	Quizartinib vs placebo	1.14 (0.62, 2.12)
RATIFY	Midostaurin vs placebo	1.25 (0.79, 1.99)
Naiive	Quizartinib vs Midostaurin	0.83 (0.44, 1.56)
MAIC	Quizartinib vs Midostaurin	0.92 (0.42, 1.97)

Source: Daiichi Sankyo, 2023 (7).

Cumulative incidence of relapse

Matching shifted the CIR curve for quizartinib downwards, while the placebo for Q-F upwards, improving the relative effectiveness of quizartinib after matching.

Matching shifted downwards the quizartinib CIR KM curve, as indicated by the resulting HR and as shown in Figure 22. CIR endpoints for both Q-F and RATIFY are presented in sections 6.1.4.3 and 6.1.5.4, respectively.

Table 61 Summary of CIR HR (Q-F ≤60 y.o and RATIFY FLT3-ITD+ populations)

Data	Comparison	HR (95% CI)
Q-F unadjusted	Quizartinib vs placebo	0.49 (0.28, 0.86)

Q-F adjusted	Quizartinib vs placebo	0.34 (0.17, 0.66)
RATIFY	Midostaurin vs placebo	0.80 (0.56, 1.15)
Naiive	Quizartinib vs Midostaurin	0.61 (0.31, 1.19)
MAIC	Quizartinib vs Midostaurin	0.42 (0.20, 0.91)

Source: Daiichi Sankyo, 2023 (7).

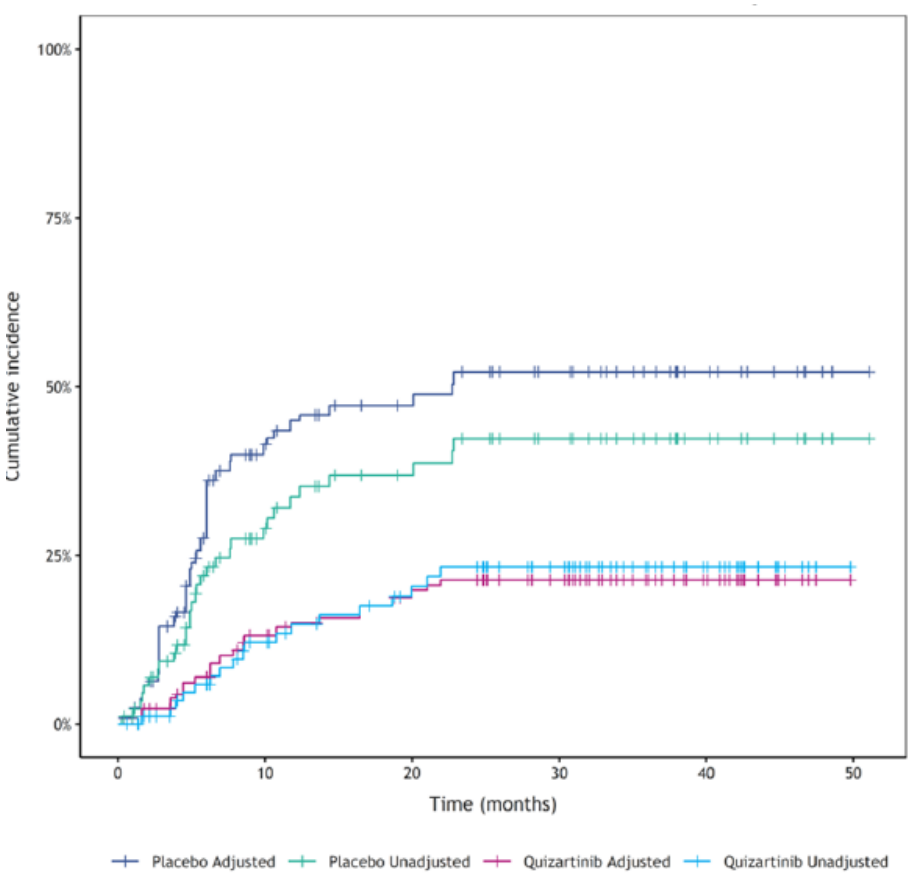

Figure 22 Matched and unmatched Q-F ≤ 60 years old CIR (with RATIFY ITD+)

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Source: Daiichi Sankyo, 2023 (7).

In Table 62, the HR and OR for each study endpoints, before and after matching when relevant, are summarised.

Table 62 Comparative analysis of studies comparing quizartinib to midostaurin for patients with *FLT3*-ITD+ AML

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
OS (quizartinib vs. placebo, unadjusted)	Q-F	N/A	N/A	N/A	HR: 0.68	0.50–0.94	N/A	HR and 95% CI from stratified Cox PH model.	NO
OS (quizartinib vs. placebo, weighted)	Q-F	N/A	N/A	N/A	HR: 0.65	0.42–1.00	N/A	HR from weighted Cox PH model. CI was computed using the robust sandwich variance estimation.	NO
OS (midostaurin vs. placebo)	RATIFY	N/A	N/A	N/A	HR: 0.79	0.59–1.06	N/A	HR and 95% CI from stratified Cox PH model.	NO
OS (quizartinib vs. midostaurin, naïve)	Q-F and RATIFY	N/A	N/A	N/A	HR: 0.87	0.56–1.34	N/A	The patient populations of RATIFY and Q-F were directly compared without matching by using log HR and its standard errors.	NO
OS (quizartinib vs. midostaurin, MAIC)	Q-F and RATIFY	N/A	N/A	N/A	HR: 0.82	0.48–1.39	N/A	CI was computed using the robust sandwich variance estimation.	YES
CR (quizartinib vs. placebo, unadjusted)	Q-F	N/A	N/A	N/A	OR: 1.04	0.67–1.60	N/A	OR based on weighted logistic regression with binomial link. CI was computed using	NO

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
								the robust sandwich variance estimation.	
CR (quizartinib vs. placebo, weighted)	Q-F	N/A	N/A	N/A	OR: 1.14	0.62–2.12	N/A	OR based on weighted logistic regression with binomial link. CI was computed using the robust sandwich variance estimation.	NO
CR (midostaurin vs. placebo)	RATIFY	N/A	N/A	N/A	OR: 1.25	0.79–1.99	N/A	OR based on weighted logistic regression with binomial link. CI was computed using the robust sandwich variance estimation	NO
CR (quizartinib vs. midostaurin, naïve)	Q-F and RATIFY	N/A	N/A	N/A	OR: 0.83	0.44–1.56	N/A	The patient populations of RATIFY and Q-F were directly compared without matching by using log OR and its standard errors.	NO
CR (quizartinib vs. midostaurin, MAIC)	Q-F and RATIFY	N/A	N/A	N/A	OR: 0.92	0.42–1.97	N/A	OR based on weighted logistic regression with binomial link. CI was computed using the robust	NO

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
								sandwich variance estimation	
CIR (quizartinib vs. placebo, unadjusted)	Q-F	N/A	N/A	N/A	HR: 0.49	0.28–0.86	N/A	HR and 95% CI from competing risk model with death as competing risk.	NO
CIR (quizartinib vs. placebo, weighted)	Q-F	N/A	N/A	N/A	HR: 0.34	0.17–0.66	N/A	HR from weighted competing risk model with death as competing risk. CI was computed using the robust sandwich variance estimation.	NO
CIR (midostaurin vs. placebo)	RATIFY	N/A	N/A	N/A	HR: 0.80	0.56–1.15	N/A	HR and 95% CI from competing risk model with death as a competing risk based on Table 3 in Rücker (3).	NO
CIR (quizartinib vs. midostaurin, naïve)	Q-F and RATIFY	N/A	N/A	N/A	HR: 0.61	0.31–1.19	N/A	The patient populations of RATIFY and Q-F were directly compared without matching by using log HR and its standard errors.	NO
CIR (quizartinib vs. midostaurin, MAIC)	Q-F and RATIFY	N/A	N/A	N/A	HR: 0.42	0.20–	N/A	CI was computed using the robust	YES

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
						0.91		sandwich variance estimation.	

Notes: A MAIC OS HR < 1 favours quizartinib. A MAIC CR OR > 1 favours quizartinib. A MAIC CIR HR < 1 favours quizartinib.
Source: Daiichi Sankyo, 2023, table 18, table 19 and table 20 (7).

Appendix D. Extrapolation

The survival analysis was performed for two populations:

1. Base case: The weighted Q-F population of age ≤ 60 years matched to the RATIFY FLT3-ITD+ population. The weights used were matched based on four treatment effect modifiers, namely, age, sex, platelet count and NPM1 positive mutation status (see description of the MAIC in section 7 and Appendix C.

2. The naïve Q-F ITT population, used in the Naïve scenario.

Time to event data for Relapse and Death for patients in CRc were collected directly in Q-F for quizartinib and SC. As SC was not included as a comparator, SC extrapolations were not leveraged in this appraisal.

The RFS endpoint extrapolated in the economic model is for patients in CRc. To account for competing risks, patients which died or began receiving HSCT were censored. Individuals receiving HSCT were censored at the start date of the conditioning regimen. For simplicity this endpoint will be referred to "Relapse after CRc".

The Death endpoint extrapolated in the economic model is also for patients in CRc, which is defined as the time between the date patients enter first CRc and the date of death due to any cause. Patients who relapse or receive HSCT are censored, and patients who did not progress, die, or receive HSCT, are censored on the last known date alive. For simplicity this endpoint will be referred to "Death after CRc".

Both separately fitted and jointly fitted survival curves were considered for inclusion in the economic model.

Seven functional forms (exponential, Weibull, log-normal, log-logistic, Gompertz, gamma and generalized gamma) were used to fit survival curves for each endpoint and treatment. The survival curves were evaluated based on the following criteria:

- Visual fit – comparing the extrapolated curves to the KM curves and smoothed hazard plots to observed hazards
- Statistical criteria – comparing Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics among curve fits; lower AIC and/or BIC indicate better agreement with the data
- Face validity and clinical plausibility:
    - Checking that selected Relapse do not cross the selected Death curve.
    - Evaluating median estimates in the observed data and in the extrapolations, when possible.

The most representative model fit for each treatment and endpoint was selected for the base case analysis.

In model calculations, the risk of death at each model cycle was constrained to be no lower than the age- and sex-specific general population mortality in Denmark.

In addition, a cure point was implemented at year 3. With the cure approach, patients who remain in the CR1 and post-HSCT maintenance 1L health states beyond 3 years are assumed to be cured. Cure was implemented by setting the probability of relapse from these health states to zero (i.e. Relapse was assumed to remain constant until death) and setting

the mortality rate from CR1 equal to the general population mortality (adjusted with a twofold increase in line with the NICE TA523). Patients who entered the refractory, relapse, and post-HSCT relapse health states were not considered to be curable. Three years was selected as the cure point as this is when the Death curves flattened and is also in line with prior TAs in AML (TA523) .Three years was selected as the cure point as this is when the Death curves flattened and is also in line with prior TAs in AML (TA523) (4).

After the cure point it was assumed that patients in these health states do not accrue disease management costs and utilities were assumed to be the same as those of the age and gender adjusted general population (HSE, 2014) (75). After the cure point it was assumed that patients in these health states do not accrue disease management costs and utilities were assumed to be the same as those of the age and gender adjusted general population (HSE, 2014) (75).

D.1 Adjusted Q-F population – Relapse after CRc

D.1.1 Data input

The KM curves for "Relapse after CRc" are shown in Figure 23. Median Relapse after CRc in the quizartinib arm of Q-F was [redacted] (95% CI: [redacted] to [redacted]). In the QuANTUM-First trial, RFS was defined as the time, for patients who achieved CRc during induction, until the date of documented relapse or death from any cause, whichever occurred first. However, as Figure 23 are used to inform the transition from CR1 to Relapse1 health state, they are referred to as Relapse after CRc curves rather than RFS curves. In addition, to account for competing risks, patients that died or began receiving HSCT were censored. Individuals receiving HSCT were censored at the start date of the conditioning regimen.

Figure 23 SC and quizartinib KM - Relapse after CRc

Notes: Placebo refers to SC in the figure. Number at risk are also refer to the adjusted population

D.1.2 Model

The KM estimates for the quizartinib arm and the seven fitted parametric models are shown in Figure 24. The models were fitted and evaluated for use in the base case analysis using the methods detailed above.

Figure 24 Independent models, quizartinib - "Relapse after CRc"

D.1.3 Proportional hazards

In the Schoenfeld residual plot (Figure 25) suggests a violation of the PH, as the trend line do not lie on a straight line. The Schoenfeld residual test also indicate a violation of the proportional hazards (p value < 0.05). The log-cumulative hazard curves do not appear parallel. Rather, they converge (Figure 26). The proportional hazard assumption was therefore considered not to hold. There for independent models were considered appropriate. As the SC arm is not used in the appraisal, the information below focus on the quizartinib arm.

Figure 25 Schoenfeld residual plot - “Relapse after CRc”

Figure 26 Log-cumulative hazards plot - “Relapse after CRc”

D.1.4 Evaluation of statistical fit (AIC and BIC)

AIC and BIC statistics for each model are presented in Table 63. For quizartinib, the exponential provides the lower AIC and BIC values, followed by log-normal and loglogistic.

Table 63 AIC and BIC for Relapse after CRc

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

D.1.5 Evaluation of visual fit

All model seems to fit well the quizartinib KM curve up to approximately 1.5 years while overestimate the portion between 1.5 and 3 years. Thereafter, exponential, gamma, log-logistic and Weibull fail to fit the tail of the KM, where lognormal generalised gamma and Gompertz appear to have a better fit.

D.1.6 Evaluation of hazard functions

In the quizartinib arm, generalized gamma, Gompertz, and log-normal fit satisfactorily to the observed smoothed hazard curve, however, all models failed to capture the declining trajectory of the curve toward the end of the observed data.

Figure 27 Smoothed hazard plots –Relapse after CRc

Notes: Placebo refers to SC in the figure

D.1.7 Adjustment of background mortality

Throughout the model, the mortality rate is set to be at least that of the age- and sex adjusted general population in Denmark.

D.1.8 Adjustment for treatment switching/cross-over

Not applicable

D.1.9 Waning effect

Not applicable

D.1.10 Cure-point

See description at the beginning of this appendix

D.1.11 Validation and discussion of extrapolated curves

AIC and BIC are least for exponential, log-normal and log-loglogistic. Visually, where log-normal generalised gamma and Gompertz appear to better fit. Out of these 5 distributions, log-normal fit satisfactorily to the observed smoothed hazard curve and was therefore selected for the base case.

Median "Relapse from CRc" by HSCT in the quizartinib arm of Q-F was not reached (95% CI: [redacted]) months and was therefore not possible to compare this with the extrapolated data. No external data was identified to further validate the extrapolations of this endpoint. In addition, the cure-point was within the trial follow-up more emphasis was put on the fit statistical and visual fit during the trial follow up than long-term plausibility

D.2 Adjusted Q-F population - Death after CRc

D.2.1 Data input

The KM curves for "Death from CRc" for HSCT are shown in Figure 28. The median was not reached in either the quizartinib or SC arm.

Figure 28 SC and quizartinib KM - Death after CRc

Notes: Placebo refers to SC in the figure. Number at risk are also refer to the adjusted population

D.2.2 Model

The KM estimates for the quizartinib arm and the seven fitted parametric models are shown in Figure 29. The Gompertz distribution did not converge during the fitting process.

Figure 29 Independent models, quizartinib – Death after CRc

D.2.3 Proportional hazards

The Schoenfeld residual plot (Figure 30) suggests a violation of the PH, as the trend line do not lie on a straight line. The Schoenfeld residual test instead do not indicate a violation of the proportional hazards (p value > 0.05). On the other side, the log-cumulative hazard curves do not appear parallel. Rather, they cross multiple times (Figure 31). The proportional hazard assumption was therefore considered not to hold, and independent models were considered appropriate. As the SC arm is not used in the appraisal, the information below focus on the quizartinib arm.

Figure 30 Schoenfeld residual plot – "Death from CRc"

Figure 31 Log-cumulative hazards plot –Death after CRc

D.2.4 Evaluation of statistical fit (AIC and BIC)

AIC and BIC statistics for each model are presented in Table 69. Similarly, as for Relapse, for quizartinib, the exponential provides the lower AIC and BIC values, followed by log-normal and log-logistic.

Table 64 AIC and BIC for Death from CRc censored

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

D.2.5 Evaluation of visual fit

The exponential appears to overestimate the KM curve in the first year of the follow-up and underestimate it thereafter. Log-normal and log-logistic have similar visual fit, with log-logistic providing slightly lower estimates at the end of the follow-up. Gamma and Weibull appear very close to the log-logistic estimates.

D.2.6 Evaluation of hazard functions

None of the model fit very well the observed data, nevertheless, log-normal has an acceptable fit. Log-logistic present higher hazards at the beginning of the follow-up, similarly to the generalised gamma, while the exponential have lower hazard at the start of the time horizon.

Figure 32 Smoothed hazard plots - Death after CRc

Notes: Placebo refers to SC in the figure

D.2.7 Adjustment of background mortality

Death after CRc extrapolations are adjusted for the Danish general population mortality

D.2.8 Adjustment for treatment switching/cross-over

Not applicable

D.2.9 Waning effect

Not applicable

D.2.10 Cure-point

See description at the beginning of this appendix

D.2.11 Validation and discussion of extrapolated curves

The curves with best statistical fit were the exponential, log-normal and log-logistic. Visually the exponential underestimated the KM curve after approximately 1 year. Log-normal and log-logistic had similar visual fit, but the log-logistic failed to match the hazard trend of the observed data at the start of the follow-up. Log-normal was therefore selected as base case distribution

Median Death after CRc by HSCT in the quizartinib arm of Q-F was not reached and was therefore not possible to compare this with the extrapolated data. No external data was identified to further validate the extrapolations of this endpoint. In addition, the cure-point was within the trial follow-up more emphasis was put on the fit statistical and visual fit during the trial follow up than long-term plausibility

D.3 Naïve Q-F population – Relapse after CrC

D.3.1 Data input

The KM curves for Relapse for patients in CRc censored are shown in Figure 33. Median "Relapse from CRc" in the quizartinib arm of Q-F was [redacted] (95% CI: [redacted] to [redacted]).

The figures show the curves almost crossing between 3 and 6 months, to then diverge between 6 and 21 months. After approximately 24 months, both curves appear to plateau.

Figure 33 KM curves - Relapse after CRc – Naïve

Notes: Placebo refers to SC in the figure.

D.3.2 Model

The KM estimates for the quizartinib arm and the seven fitted parametric models are shown in Figure 34.

Figure 34 Independent models, quizartinib –Relapse after CRc – Naïve

D.3.3 Proportional hazards

In the Schoenfeld residual plot (Figure 35) suggests a violation of the PH, as the trend line do not lie on a straight line. The Schoenfeld residual test do not clearly indicate a violation of the proportional hazards (p value > 0.05). The log-cumulative hazard curves do not appear parallel (Figure 36). The proportional hazard assumption was therefore considered not to hold and the use of independent models was considered appropriate. As the SC arm is not used in the appraisal, the information below focus on the quizartinib arm.

Figure 35 Schoenfeld residual plot - Relapse after CRc – Naïve

Figure 36 Log-cumulative hazards plot - Relapse after CRc -Naïve

D.3.4 Evaluation of statistical fit (AIC and BIC)

Table 65 presents the AIC and BIC scores for the independent models for quizartinib. Log-normal, loglogistic and exponential distributions have the lowest combined AIC and BIC value.

Table 65 AIC and BIC for independent models for quizartinib and SC - Relapse after CR censored for HSCT

	Quizartinib	
	AIC	BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; SC = SC

D.3.5 Evaluation of visual fit

In the quizartinib arm, all model estimates well the first 2 years of the time horizon, as well as all fail representing the tail of the KM curve, which suggest the start of a plateau. Log-normal and generalised gamma were considered to have an acceptable visual fit balancing the survival estimation between 2 and 4 years.

D.3.6 Evaluation of hazard functions

Figure 37 presents the smoothed hazard curves. In the quizartinib arm, log-logistic, log-normal, Gompertz, and generalized gamma showed acceptable fits to observed hazards over time.

Figure 37 Smoothed hazard plots - Relapse after CRc – Naïve

Notes: Placebo refers to SC in the figure.

D.3.7 Adjustment of background mortality

Throughout the economic model, the mortality rate is set to be at least that of the age- and sex adjusted general population in Denmark.

D.3.8 Adjustment for treatment switching/cross-over

Not applicable

D.3.9 Waning effect

Not applicable

D.3.10 Cure-point

See description at the beginning of this appendix

D.3.11 Validation and discussion of extrapolated curves

Log-normal had the least AIC and BIC scores. In conjunction with visual fit and the hazards trend, it was selected for the based case.

Median “Relapse from CRc” by HSCT in the quizartinib arm of Q-F was [redacted] months (95% CI [redacted]). The curved with an estimated median closer to the observed data were log-logistic ([redacted] months), log-normal ([redacted] months) and gamma ([redacted]). Of these, log-normal had the best statistical fit.

No external data was identified to further validate the extrapolations of this endpoint .In addition, the cure-point was within the trial follow-up more emphasis was put on the fit statistical and visual fit during the trial follow up than long-term plausibility

D.4 Naïve Q-F population - Death after CRc

D.4.1 Data input

The KM curves for "Death from CRc" for HSCT are shown in Figure 38. The median was not reached in either the quizartinib or SC arm.

Figure 38 KM curves –Death after CRc for HSCT – Naïve

Notes: Placebo refers to SC in the figure

D.4.2 Model

The KM estimates for the quizartinib arm and the seven fitted parametric models are shown in Figure 39.

Figure 39 Independent models, quizartinib – Death after CRc censored

D.4.3 Proportional hazards

In the Schoenfeld residual plot (Figure 40) suggests a violation of the PH, as the trend line do not lie on a straight line. The Schoenfeld residual test instead do not indicate a violation of the proportional hazards (p value > 0.05). On the other side, the log-cumulative hazard curves do not appear parallel. Rather, they cross multiple times (Figure 41). The proportional hazard assumption was therefore considered not to hold, and independent models were considered appropriate. As the SC arm is not used in the appraisal, the information below focus on the quizartinib arm.

Figure 40 Schoenfeld residual plot –Death after CRc

Figure 41 Log-cumulative hazards plot –Death after CRc

D.4.4 Evaluation of statistical fit

AIC and BIC statistics for each model are presented in Table 71. The exponential provides the lower AIC and BIC values, followed by log-normal and Weibull.

Table 66 AIC and BIC for Death after CRc censored

	quizartinib	
	AIC	BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

D.4.5 Evaluation of visual fit

All curves have similar visual fit up to ~1.5 years of the follow-up., when they start to diverge. Generalised gamma and exponential appear to over and underestimate the KM curve thereafter, while log-normal, log-logistic, Weibull and gamma appear to have similar visual fit.

D.4.6 Evaluation of hazard functions

The log-normal appear to best follow the hazard trend. Log-logistic, Weibull and gamma overestimate the hazards towards the end of the follow up. Also, the exponential does not provide good fit to the observed data. The hazards at the start of the follow-up are overestimated from the gamma distribution, as well as the generalised gamma.

Figure 42 Smoothed hazard plots –Death after CRc – Naïve

Notes: Placebo refers to SC in the figure

D.4.7 Adjustment of background mortality

Death from CRc extrapolations are adjusted for the Danish general population mortality

D.4.8 Adjustment for treatment switching/cross-over

Not applicable

D.4.9 Waning effect

Not applicable

D.4.10 Cure-point

See description at the beginning of this appendix

D.4.11 Validation and discussion of extrapolated curves

The curves with best statistical fit were the exponential, log-normal and Weibull.

Visually, log-normal, log-logistic, Weibull and gamma appear to have similar visual fit, while the exponential seem to underestimate the KM curve after ~1 year.

Log-normal appeared to be the best distribution matching the observed hazards, therefore was selected in the base case.

Median "Death from CRc" by HSCT in the quizartinib arm of Q-F was not reached and was therefore not possible to compare this with the extrapolated data. No external data was identified to further validate the extrapolations of this endpoint .In addition, the cure-point was within the trial follow-up more emphasis was put on the fit statistical and visual fit during the trial follow up than long-term plausibility.

Appendix E. Serious adverse events

Table 67 presents treatment-emergent SAEs in Q-F (patients <60 years) by system organ class and preferred term.

Table 67 treatment-emergent SAEs in ≥1% of subjects <60 years in Q-F (13-08-2021)

System organ class Preferred term	Quizartinib (N=159) n (%)	Placebo (N=160) n (%)
Any treatment-emergent SAEs	**84 (52.8)**	**64 (40.0)**
Infections and infestations	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Pneumonia fungal	[redacted]	[redacted]
Coronavirus disease 2019	[redacted]	[redacted]
Klebsiella sepsis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Pseudomonas infection	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Klebsiella bacteraemia	[redacted]	[redacted]
Mucormycosis	[redacted]	[redacted]
Streptococcal sepsis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Staphylococcal sepsis	[redacted]	[redacted]
Escherichia sepsis	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Myelosuppression	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Graft-versus-host disease in gastrointestinal tract	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Brain oedema	[redacted]	[redacted]

System organ class Preferred term	Quizartinib (N=159) n (%)	Placebo (N=160) n (%)
Cardiac disorders	[redacted]	[redacted]
Pericarditis	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Anal fistula	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Neutropenic colitis	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Hepatic cytolysis	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Osteonecrosis	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

Note: If a subject had more than 1 event per system organ class (or preferred term) level, the subject was counted once at each level of summation.
Source: Daiichi Sankyo, 2022, table 14.3.2.1.4 (8)

Table 68 presents treatment-emergent SAEs in Q-F by system organ class and preferred term for the ITT population.

Table 68 treatment-emergent SAE* in ≥1% of subjects in Q-F (13-08-2021)

System organ class Preferred term	Quizartinib (N=265) n (%)	Placebo (N=268) n (%)
Any treatment-emergent SAE	**143 (54.0)**	**123 (45.9)**
Infections and infestations	[redacted]	[redacted]
Pneumonia	17 (6.4)	15 (5.6)
Septic shock	11 (4.2)	8 (3.0)
Sepsis	10 (3.8)	14 (5.2)
Klebsiella sepsis	7 (2.6)	1 (0.4)
Herpes zoster	5 (1.9)	1 (0.4)
Pneumonia fungal	4 (1.5)	1 (0.4)

System organ class Preferred term	Quizartinib (N=265) n (%)	Placebo (N=268) n (%)
Urinary tract infection	3 (1.1)	2 (0.7)
Coronavirus disease 2019	3 (1.1)	0
Staphylococcal sepsis	1 (0.4)	3 (1.1)
Device related infection	0	3 (1.1)
Blood and lymphatic system disorders	[redacted]	[redacted]
Febrile neutropenia	29 (10.9)	22 (8.2)
Neutropenia	4 (1.5)	5 (1.9)
Myelosuppression	3 (1.1)	0
Thrombocytopenia	2 (0.8)	8 (3.0)
Leukopenia	0	3 (1.1)
Gastrointestinal disorders	[redacted]	[redacted]
Anal fistula	4 (1.5)	0
Colitis	3 (1.1)	3 (1.1)
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Respiratory failure	3 (1.1)	3 (1.1)
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	8 (3.0)	5 (1.9)
Investigations	[redacted]	[redacted]
Neutrophil count decreased	4 (1.5)	0
Cardiac disorders	[redacted]	[redacted]
Atrial fibrillation	1 (0.4)	3 (1.1)
Pericarditis	0	3 (1.1)
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	4 (1.5)	2 (0.7)
Immune system disorders	[redacted]	[redacted]
Graft-versus-host disease in gastrointestinal tract	4 (1.5)	0
Nervous system disorders	[redacted]	[redacted]
Cerebrovascular accident	0	3 (1.1)

Note: Denominator for percentages was the number of subjects in the Safety Analysis Set. If a subject had more than 1 event per system organ class (or preferred term) level, the subject was counted once at each level of summation.
Source: Daiichi Sankyo, 2022, table 10.14 (8)

Table 69 presents SAEs reported in and RATIFY.

Table 69 SAEs* in ≥1% of subjects in RATIFY (July 2016)

	Midostaurin (N=355) n (%)	Placebo (N=354) n (%)
Any SAE	**157 (44.2)**	**154 (43.5)**
Blood and lymphatic system disorders	**N/A**	**N/A**
Febrile neutropenia	105 (29.6)	110 (31.1)
Haemoglobin decreased	154 (43.4)	148 (41.8)
Lymphatic disorder	6 (1.7)	4 (1.1)
Cardiac disorders	**N/A**	**N/A**
Atrial fibrillation	4 (1.1)	6 (1.7)
Cardiac disorder	4 (1.1)	6 (1.7)
Left ventricular failure	8 (2.3)	7 (2.0)
Pericardial effusion	4 (1.1)	5 (1.4)
Sinus tachycardia	17 (4.8)	15 (4.2)
Eye disorders	**N/A**	**N/A**
Eye disorder	8 (2.3)	12 (3.4)
Keratitis	5 (1.4)	8 (2.3)
Vision blurred	2 (0.6)	4 (1.1)
Gastrointestinal disorders	**N/A**	**N/A**
Abdominal distension	4 (1.1)	2 (0.6)
Abdominal pain	29 (8.2)	28 (7.9)
Anal pain	7 (2.0)	5 (1.4)
Colitis	9 (2.5)	9 (2.5)
Constipation	16 (4.5)	17 (4.8)
Diarrhoea	89 (25.1)	89 (25.1)
Dyspepsia	10 (2.8)	8 (2.3)
Dysphagia	10 (2.8)	10 (2.8)
Ear, nose, and throat examination abnormal	40 (11.3)	42 (11.9)
Flatulence	7 (2.0)	5 (1.4)
Gastrointestinal disorder	10 (2.8)	10 (2.8)
Haemorrhoids	11 (3.1)	7 (2.0)
Ileus	2 (0.6)	4 (1.1)
Mucositis oral	23 (6.5)	11 (3.1)
Nausea	98 (27.6)	91 (25.7)
Oral haemorrhage	5 (1.4)	10 (2.8)
Oral pain	5 (1.4)	5 (1.4)
Stomach pain	8 (2.3)	9 (2.5)

	Midostaurin (N=355) n (%)	Placebo (N=354) n (%)
Toothache	3 (0.9)	4 (1.1)
Vomiting	70 (19.7)	65 (18.4)
General disorders	**N/A**	**N/A**
Chest pain	6 (1.7)	11 (3.1)
Chills	16 (4.5)	16 (4.5)
Oedema limbs	26 (7.3)	21 (5.9)
Fatigue	95 (26.8)	98 (27.7)
Fever	34 (9.6)	33 (9.3)
General symptom	11 (3.1)	15 (4.2)
Ill-defined disorder	1 (0.3)	4 (1.1)
Injection site reaction	14 (3.9)	17 (4.8)
Localized oedema	5 (1.4)	9 (2.5)
Multi-organ failure	4 (1.1)	5 (1.4)
Pain	14 (3.9)	18 (5.1)
Hepatobiliary disorders	**N/A**	**N/A**
Hepatobiliary disease	4 (1.1)	1 (0.3)
Immune system disorders	**N/A**	**N/A**
Hypersensitivity	7 (2.0)	14 (4.0)
Infections and infestations	**N/A**	**N/A**
Anal infection	6 (1.7)	5 (1.4)
Catheter related infection	29 (8.2)	21 (5.9)
Conjunctivitis infective	4 (1.1)	3 (0.9)
Infection	30 (8.5)	26 (7.3)
Infectious colitis	8 (2.3)	9 (2.5)
Lip infection	5 (1.4)	8 (2.3)
Pneumonia	25 (7.0)	35 (9.9)
Sepsis	23 (6.5)	16 (4.5)
Skin infection	8 (2.3)	8 (2.3)
Soft tissue infection	0	4 (1.1)
Tooth infection	1 (0.3)	4 (1.1)
Urinary tract infection	8 (2.3)	15 (4.2)
Wound infection	4 (1.1)	2 (0.6)
Investigations	**N/A**	**N/A**
Activated partial thromboplastin time prolonged	9 (2.5)	9 (2.5)
Alanine aminotransferase increased	35 (9.9)	35 (9.9)

	Midostaurin (N=355) n (%)	Placebo (N=354) n (%)
Alkaline phosphatase increased	8 (2.3)	20 (5.7)
Aspartate aminotransferase increased	30 (8.5)	29 (8.2)
Blood bilirubin increased	25 (7.0)	36 (10.2)
Coagulopathy	8 (2.3)	7 (2.0)
Creatinine increased	15 (4.2)	16 (4.5)
Electrocardiogram QTc interval prolonged	17 (4.8)	19 (5.4)
Fibrinogen decreased	2 (0.6)	7 (2.0)
Gamma-glutamyl transferase increased	19 (5.4)	22 (6.2)
International normalised ratio increased	8 (2.3)	5 (1.4)
Laboratory test abnormal	18 (5.1)	28 (7.9)
Leukocyte count decreased	41 (11.6)	47 (13.3)
Lymphocyte count decreased	22 (6.2)	36 (10.2)
Neutrophil count decreased	145 (40.9)	146 (41.2)
Platelet count decreased	155 (43.7)	146 (41.2)
Weight loss	1 (0.3)	11 (3.1)
Metabolism and nutrition disorders	**N/A**	**N/A**
Anorexia	21 (5.9)	26 (7.3)
Blood glucose increased	17 (4.8)	22 (6.2)
Blood uric acid increased	6 (1.7)	4 (1.1)
Serum albumin decreased	19 (5.4)	22 (6.2)
Serum calcium decreased	20 (5.6)	26 (7.3)
Serum magnesium decreased	15 (4.2)	15 (4.2)
Serum phosphate decreased	7 (2.0)	12 (3.4)
Serum potassium decreased	31 (8.7)	47 (13.3)
Serum potassium increased	8 (2.3)	4 (1.1)
Serum sodium decreased	20 (5.6)	10 (5.7)
Serum sodium increased	5 (1.4)	5 (1.4)
Musculoskeletal and connective tissue disorders	**N/A**	**N/A**
Arthralgia	8 (2.3)	6 (1.7)
Back pain	15 (4.2)	13 (3.7)
Bone pain	7 (2.0)	4 (1.1)
Musculoskeletal disorder	4 (1.1)	4 (1.1)
Myalgia	7 (2.0)	4 (1.1)
Neck pain	7 (2.0)	4 (1.1)
Pain in extremity	5 (1.4)	6 (1.7)

	Midostaurin (N=355) n (%)	Placebo (N=354) n (%)
Nervous system disorders	**N/A**	**N/A**
Dizziness	19 (5.4)	20 (5.7)
Dysgeusia	4 (1.1)	7 (2.0)
Headache	41 (11.6)	42 (11.9)
Intracranial haemorrhage	3 (0.9)	6 (1.7)
Neurological disorder not otherwise specified	9 (2.5)	4 (1.1)
Peripheral sensory neuropathy	5 (1.4)	6 (1.7)
Speech disorder	4 (1.1)	1 (0.3)
Syncope	6 (1.7)	4 (1.1)
Tremor	4 (1.1)	3 (0.9)
Psychiatric disorders	**N/A**	**N/A**
Anxiety	5 (1.4)	9 (2.5)
Confusion	4 (1.1)	3 (0.9)
Depression	2 (0.6)	12 (3.4)
Insomnia	11 (3.1)	7 (2.0)
Psychosis	4 (1.1)	2 (0.6)
Renal and urinary disorders	**N/A**	**N/A**
Haemorrhage urinary tract	2 (0.6)	6 (1.7)
Renal failure	13 (3.7)	9 (2.5)
Urogenital disorder	15 (4.2)	11 (3.11)
Reproductive system and breast disorders	**N/A**	**N/A**
Uterine haemorrhage	4 (1.1)	3 (0.9)
Vaginal haemorrhage	5 (1.4)	9 (2.5)
Respiratory, thoracic and mediastinal disorders	**N/A**	**N/A**
Adult respiratory distress syndrome	9 (2.5)	5 (1.4)
Cough	17 (4.8)	19 (5.4)
Dyspnoea	20 (5.6)	24 (6.8)
Epistaxis	24 (6.8)	22 (6.2)
Hypoxia	8 (2.3)	12 (3.4)
Pharyngolaryngeal pain	6 (1.7)	11 (3.1)
Pleural effusion	8 (2.3)	8 (2.3)
Pneumonitis	27 (7.6)	17 (4.8)
Respiratory disorder	12 (3.4)	9 (2.5)
Skin and subcutaneous tissue disorders	**N/A**	**N/A**
Alopecia	6 (1.7)	4 (1.1)

	Midostaurin (N=355) n (%)	Placebo (N=354) n (%)
Dry skin	7 (2.0)	7 (2.0)
Hand-and-foot syndrome	2 (0.6)	5 (1.4)
Petechiae	35 (9.9)	34 (9.6)
Pruritus	11 (3.1)	12 (3.4)
Rash desquamating	59 (16.6)	66 (18.6)
Skin disorder	23 (6.5)	23 (6.5)
Sweating	14 (3.9)	14 (4.0)
Vascular disorders	**N/A**	**N/A**
Hematoma	14 (3.9)	13 (3.7)
Haemorrhage	14 (3.9)	12 (3.4)
Hypertension	13 (3.7)	11 (3.1)
Hypotension	25 (7.0)	19 (5.4)
Phlebitis	6 (1.7)	7 (2.0)

Note: All events were collected by systematic assessment. *A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.
Source: ClinicalTrials.gov, 2008 (9).

Appendix F. Health-related quality of life

N/R

Appendix G. Probabilistic sensitivity analyses

Table 70 presents the parameters used in the model to inform the probabilistic sensitivity analysis. These parameters can be varied in the model "inputs" sheet. Note that Relapse and Death from CRc parameters are varied based on their Cholesky decompositions.

Table 70. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Female	[redacted]	[redacted]	[redacted]	Beta
Age	47.00	[redacted]	[redacted]	Lognormal
Bodyweight	[redacted]	[redacted]	[redacted]	Lognormal
Mean height (cm)	[redacted]	[redacted]	[redacted]	Lognormal
RDI				
Relative dose intensity : Quizartinib, Quizartinib	[redacted]	[redacted]	[redacted]	Beta
Relative dose intensity : Midostaurin, Midostaurin	0.95	0.76	1.00	Beta
Relative dose intensity : Midostaurin, Sorafenib	1.00	1.00	1.00	Beta
Relative dose intensity : Gilterinib	0.98	0.79	1.00	Beta
Subsequent tx, Quizartinib: Flag_Ida %	0.60	0.36	0.82	Beta
Subsequent tx, Quizartinib: Gilterinib %	0.40	0.25	0.56	Beta
Subsequent tx, Midostaurin: Flag_Ida %	0.40	0.25	0.56	Beta
Subsequent tx, Midostaurin: Gilterinib %	0.60	0.36	0.82	Beta
% using treatment post-HSCT:Quizartinib	[redacted]	[redacted]	[redacted]	Beta
% using treatment post-HSCT:Sorafenib (after Mido)	[redacted]	[redacted]	[redacted]	Beta
Incidence AE				
Quizartinib: AE: Incidence (%) - Anemia	0.06	0.04	0.08	Beta
Quizartinib: AE: Incidence (%) - Diarrhea	0.04	0.02	0.05	Beta
Quizartinib: AE: Incidence (%) - Fatigue	0.00	0.00	0.01	Beta
Quizartinib: AE: Incidence (%) - Febrile neutropenia	0.45	0.28	0.63	Beta
Quizartinib: AE: Incidence (%) - Hyperbilirubinemia	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Hypocalcemia	0.00	0.00	0.00	Beta

Quizartinib: AE: Incidence (%) - Hypokalemia	0.17	0.11	0.24	Beta
Quizartinib: AE: Incidence (%) - Hyponatremia	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Hypophosphatemia	0.06	0.04	0.08	Beta
Quizartinib: AE: Incidence (%) - Increased alanine aminotransferase	0.04	0.03	0.06	Beta
Quizartinib: AE: Incidence (%) - Infection	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Leukopenia	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Lymphopenia	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Mucositis or stomatitis	0.05	0.03	0.07	Beta
Quizartinib: AE: Incidence (%) - Nausea	0.01	0.00	0.01	Beta
Quizartinib: AE: Incidence (%) - Neutropenia	0.18	0.11	0.25	Beta
Quizartinib: AE: Incidence (%) - Pain	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Pneumonitis or pulmonary infiltrates	0.11	0.07	0.16	Beta
Quizartinib: AE: Incidence (%) - Rash or desquamation	0.03	0.02	0.04	Beta
Quizartinib: AE: Incidence (%) - Thrombocytopenia	0.08	0.05	0.12	Beta
Quizartinib: AE: Incidence (%) - Neutrophil count decreased	0.11	0.00	0.41	Beta
Quizartinib: AE: Incidence (%) - Sepsis	0.04	0.01	0.10	Beta
Quizartinib: AE: Incidence (%) - Gamma-glutamyl transferase increased	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Platelet count decreased	[redacted]	[redacted]	[redacted]	Beta
Quizartinib: AE: Incidence (%) - Hypertension	0.00	0.00	0.00	Beta
Quizartinib: AE: Incidence (%) - GVHD (post-HSCT event)	0.56	0.34	0.77	Beta
Midostaurin: AE: Incidence (%) - Anemia	0.93	0.24	1.00	Beta
Midostaurin: AE: Incidence (%) - Diarrhea	0.16	0.10	0.23	Beta
Midostaurin: AE: Incidence (%) - Fatigue	0.09	0.06	0.13	Beta

Midostaurin: AE: Incidence (%) - Febrile neutropenia	0.82	0.40	1.00	Beta
Midostaurin: AE: Incidence (%) - Hyperbilirubinemia	0.07	0.05	0.10	Beta
Midostaurin: AE: Incidence (%) - Hypocalcemia	0.07	0.04	0.10	Beta
Midostaurin: AE: Incidence (%) - Hypokalemia	0.14	0.09	0.20	Beta
Midostaurin: AE: Incidence (%) - Hyponatremia	0.09	0.06	0.13	Beta
Midostaurin: AE: Incidence (%) - Hypophosphatemia	0.05	0.04	0.07	Beta
Midostaurin: AE: Incidence (%) - Increased alanine aminotransferase	0.13	0.08	0.18	Beta
Midostaurin: AE: Incidence (%) - Infection	0.52	0.32	0.72	Beta
Midostaurin: AE: Incidence (%) - Leukopenia	0.26	0.17	0.37	Beta
Midostaurin: AE: Incidence (%) - Lymphopenia	0.19	0.12	0.27	Beta
Midostaurin: AE: Incidence (%) - Mucositis or stomatitis	0.06	0.04	0.09	Beta
Midostaurin: AE: Incidence (%) - Nausea	0.06	0.04	0.08	Beta
Midostaurin: AE: Incidence (%) - Neutropenia	0.95	0.07	1.00	Beta
Midostaurin: AE: Incidence (%) - Pain	0.13	0.09	0.19	Beta
Midostaurin: AE: Incidence (%) - Pneumonitis or pulmonary infiltrates	0.08	0.05	0.11	Beta
Midostaurin: AE: Incidence (%) - Rash or desquamation	0.14	0.09	0.20	Beta
Midostaurin: AE: Incidence (%) - Thrombocytopenia	0.97	0.97	0.97	Beta
Midostaurin: AE: Incidence (%) - Neutrophil count decreased	0.00	0.00	0.00	Beta
Midostaurin: AE: Incidence (%) - Sepsis	0.00	0.00	0.00	Beta
Midostaurin: AE: Incidence (%) - Gamma-glutamyl transferase increased	0.00	0.00	0.00	Beta
Midostaurin: AE: Incidence (%) - Platelet count decreased	0.00	0.00	0.00	Beta

Midostaurin: AE: Incidence (%) - Hypertension	0.00	0.00	0.00	Beta
Midostaurin: AE: Incidence (%) - GVHD (post-HSCT event)	0.39	0.24	0.55	Beta
GVHD disutility				
AE: Disutility (positive) - GVHD (post-HSCT event)	0.17	0.11	0.25	Beta
AE: Disutility (positive) - GVHD (post-HSCT event): Duration (days)	57.00	36.89	81.42	Gamma
Cure point (cycle)	39.13	39.13	39.13	None
Midostaurin HR				
Relapse from CRc in the non-HSCT cohort HR: Midostaurin	0.42	0.20	0.91	Lognormal
Death from CRc in the non-HSCT cohort HR: Midostaurin	0.82	0.48	1.39	Lognormal
Mean treatment duration				
Quizartinib:Induction,Mean treatment duration (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Quizartinib:Consolidation,Mean treatment duration (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Quizartinib:Maintenance,Mean treatment duration (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Quizartinib:HSCT recovery,Mean treatment duration (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Quizartinib:Maintenance, post HSCT,Mean treatment duration (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Midostaurin:Induction,Mean treatment duration (cycles)	0.77	0.50	1.10	Gamma
Midostaurin:Consolidation,Mean treatment duration (cycles)	2.32	1.50	3.31	Gamma
Midostaurin:Maintenance,Mean treatment duration (cycles)	11.96	7.74	17.08	Gamma
Maximum treatment duration:Midostaurin	8.65	8.65	8.65	None
Transition probabilities				
Quizartinib-Transition probabilities (per cycle): Induction to First CR (1st induction round)	[redacted]	[redacted]	[redacted]	Beta
Quizartinib-Transition probabilities (per cycle): Induction to Refractory (1st induction round)	[redacted]	[redacted]	[redacted]	Beta
Quizartinib-Transition probabilities (per cycle): Induction to Dead (1st induction round)	[redacted]	[redacted]	[redacted]	Beta

Quizartinib-Transition probabilities (per cycle): Induction to First CR (2nd induction round)	[redacted]	[redacted]	[redacted]	Beta
Quizartinib-Transition probabilities (per cycle): Induction to Dead (2nd induction round)	[redacted]	[redacted]	[redacted]	Beta
Quizartinib-Transition probabilities (per cycle): First CR to HSCT	[redacted]	[redacted]	[redacted]	Beta
Quizartinib-Transition probabilities (per cycle): Refractory to second line CR	0.14	0.09	0.20	Beta
Quizartinib-Transition probabilities (per cycle): Refractory to Dead	0.05	0.03	0.07	Beta
Quizartinib-Transition probabilities (per cycle): First line Relapse to second line CR	0.30	0.19	0.42	Beta
Quizartinib-Transition probabilities (per cycle): First line Relapse to dead	0.05	0.03	0.07	Beta
Quizartinib-Transition probabilities (per cycle): Second line CR to Second line Relapse	0.02	0.01	0.03	Beta
Quizartinib-Transition probabilities (per cycle): Second line CR to Second line HSCT	0.12	0.08	0.18	Beta
Quizartinib-Transition probabilities (per cycle): Second line CR to Dead	0.03	0.02	0.04	Beta
Quizartinib-Transition probabilities (per cycle): Second line Relapse to Dead	0.05	0.03	0.07	Beta
Quizartinib-Transition probabilities (per cycle): HSCT post recovery Relapse	[redacted]	[redacted]	[redacted]	Beta
Quizartinib-Transition probabilities (per cycle): HSCT 2nd line post recovery Relapse	[redacted]	[redacted]	[redacted]	Beta
Midostaurin: Induction to First CR (1st induction round)	[redacted]	[redacted]	[redacted]	Lognormal
Midostaurin: Induction to Refractory (1st induction round)	[redacted]	[redacted]	[redacted]	None
Midostaurin: Induction to Dead (1st induction round)	[redacted]	[redacted]	[redacted]	None
Midostaurin: Induction to First CR (2nd induction round)	[redacted]	[redacted]	[redacted]	Lognormal
Midostaurin- Transition probabilities (per cycle): First CR to HSCT	[redacted]	[redacted]	[redacted]	Beta

HSCT tunnel states 1st line - Probability of death (per cycle): HSCT treatment 1	0.04	0.02	0.05	Beta
HSCT tunnel states 1st line - Probability of death (per cycle): HSCT treatment 2 and 3	0.04	0.03	0.06	Beta
HSCT tunnel states 1st line - Probability of death (per cycle): HSCT recovery	0.02	0.02	0.03	Beta
HSCT tunnel states 1st line - Probability of death (per cycle): Post HSCT recovery 1+	0.00	0.00	0.01	Beta
HSCT tunnel states 2nd line - Probability of death (per cycle): HSCT treatment 1	0.04	0.02	0.05	Beta
HSCT tunnel states 2nd line - Probability of death (per cycle): HSCT treatment 2 and 3	0.04	0.03	0.06	Beta
HSCT tunnel states 2nd line - Probability of death (per cycle): HSCT recovery	0.02	0.02	0.03	Beta
Disease management frequency (days per cycle)				
Treatment management activities frequency (day per cycle):Hospitalisation days (induction):Induction	22.00	14.24	31.42	Gamma
Treatment management activities frequency (day per cycle):Daytime admission:Induction	2.00	1.29	2.86	Gamma
Treatment management activities frequency (day per cycle):Outpatients visit:Induction	6.50	4.21	9.28	Gamma
Treatment management activities frequency (day per cycle):Add day > trim:Induction	14.00	9.06	20.00	Gamma
Treatment management activities frequency (day per cycle):ITD FLT3 testing:Induction	0.00	0.00	0.00	Gamma
Treatment management activities frequency (day per cycle):Placeholder 1:Induction	0.00	0.00	0.00	Gamma
Treatment management activities frequency (day per cycle):Placeholder 2:Induction	0.00	0.00	0.00	Gamma
Treatment management activities frequency (day per cycle):Placeholder 3:Induction	0.00	0.00	0.00	Gamma

Treatment management activities frequency (day per cycle):Placeholder 4:Induction	0.00	0.00	0.00	Gamma
Treatment management activities frequency (day per cycle):Hospitalisation days (cons+relapse):Refractory	23.00	14.88	32.85	Gamma
Treatment management activities frequency (day per cycle):Daytime admission:Refractory	2.00	1.29	2.86	Gamma
Treatment management activities frequency (day per cycle):Outpatients visit:Refractory	8.00	5.18	11.43	Gamma
Treatment management activities frequency (day per cycle):Add day > trim:Refractory	15.00	9.71	21.43	Gamma
Treatment management activities frequency (day per cycle):Hospitalisation days (cons+relapse):Consolidation and continuation	10.00	6.47	14.28	Gamma
Treatment management activities frequency (day per cycle):Daytime admission:Consolidation and continuation	1.00	0.65	1.43	Gamma
Treatment management activities frequency (day per cycle):Outpatients visit:Consolidation and continuation	12.00	7.77	17.14	Gamma
Treatment management activities frequency (day per cycle):Add day > trim:Consolidation and continuation	2.00	1.29	2.86	Gamma
Treatment management activities frequency (day per cycle):Daytime admission: CR1 and 2	0.50	0.32	0.71	Gamma
Treatment management activities frequency (day per cycle):Hospitalisation days (cons+relapse):Relapse 1 and 2	23.00	14.88	32.85	Gamma
Treatment management activities frequency (day per cycle):Daytime admission:Relapse 1 and 2	2.00	1.29	2.86	Gamma
Treatment management activities frequency (day per	8.00	5.18	11.43	Gamma

cycle):Outpatients visit:Relapse 1 and 2				
Treatment management activities frequency (day per cycle):Add day > trim: Relapse 1 and 2	15.00	9.71	21.43	Gamma
Treatment management activities frequency (day per cycle):Outpatients visit:HSCT recovery 2L	4.00	4.00	4.00	None
Treatment management activities frequency (day per cycle):Outpatients visit:Post HSCT 1L and 2L maintenance	0.50	0.50	0.50	None
Patients time assumptions				
Hospitalisation	[redacted]	[redacted]	[redacted]	Gamma
Daytime admission	[redacted]	[redacted]	[redacted]	Gamma
Outpatients visit	[redacted]	[redacted]	[redacted]	Gamma
HSCT	1.00	[redacted]	[redacted]	Gamma
Hospitalisation (hours per day)	[redacted]	[redacted]	[redacted]	Gamma
Daytime admission (hours)	[redacted]	[redacted]	[redacted]	Gamma
Outpatients visit (hours)	[redacted]	[redacted]	[redacted]	Gamma
HSCT time	21.00	[redacted]	[redacted]	Gamma
Time assumed for AE (average hours)	24.00	[redacted]	[redacted]	Gamma
Utilities				
Utility: Induction	[redacted]	[redacted]	[redacted]	Beta
Utility: Refractory	[redacted]	[redacted]	[redacted]	Beta
Utility: Consolidation	[redacted]	[redacted]	[redacted]	Beta
Utility: Continuation	[redacted]	[redacted]	[redacted]	Beta
Utility: First CR	[redacted]	[redacted]	[redacted]	Beta
Utility: Relapse	[redacted]	[redacted]	[redacted]	Beta
Utility: Second CR	[redacted]	[redacted]	[redacted]	Beta
Utility: Relapse 2	[redacted]	[redacted]	[redacted]	Beta
Utility: HSCT 1L	0.61	0.36	0.83	Beta
Utility: HSCT recovery 1L	0.81	0.41	1.00	Beta
Utility: Post HSCT 1L maintenance	0.83	0.40	1.00	Beta
Utility: HSCT 2L	0.55	0.33	0.76	Beta
Utility: HSCT recovery 2L	0.73	0.40	0.95	Beta
Utility: Post HSCT 2L maintenance	0.74	0.41	0.96	Beta

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

H.1.1 Objective

Two SLR's were conducted to support this submission for quizartinib; One primary SLR with searches conducted on May 9th, 2023, and one updated search conducted on July 24th, 2023. The objective of the clinical SLRs was to identify relevant clinical evidence for patients with *FLT3+* AML.

The SLRs answer the following research question: What are the clinical efficacy and safety outcomes of current 1L treatment options in adults with untreated AML that is *FLT3+*?

H.1.2 Methods

The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (76), the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance (77) for undertaking reviews in health care, the PRISMA guidelines (78) and the methods for systematic reviews as specified by the NICE (79).The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (76), the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance (77) for undertaking reviews in health care, the PRISMA guidelines (78) and the methods for systematic reviews as specified by the NICE (79).

H.1.3 Information sources

H.1.3.1 Bibliographic databases

The OVID SP® platform was used to conduct the literature searches. The OVID SP® platform is a search platform that provides standardised access to a wide range of literature databases and is an accepted tool for use in a SLR. The databases in Table 71 were used to conduct the SLR searches, which are in line with recommendations from the Cochrane Collaboration (Higgins et al., 2019) and the NICE (National Institute for Health and Care Excellence (NICE), 2022) guidance:

Table 71 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	OVID SP	1974 until today	09.05.2023
Medline*	OVID SP	1946 until today	09.05.2023 and 24.07.2023
CENTRAL	OVID SP	April 2023	09.05.2023 and 24.07.2023
CDSR	OVID SP	2005 to May 2, 2023	09.05.2023 and 24.07.2023

Notes: * Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline® Daily, Medline and Versions®

A hand-search of the reference lists of relevant studies, key SLRs, meta-analyses and network meta-analyses publications was also conducted.

H.1.3.2 Trial registries

To ensure all relevant trials are captured, searches of the registry websites provided in Table 72 for both completed and incomplete studies were undertaken.

The relevant studies that are incomplete were listed, including their status, treatments, and outcomes assessed. The result from the completed studies were cross-checked against the available publications. All relevant data pertaining to the study objectives and methods identified via these pragmatic web searches were also extracted.

Table 72 Trial registries included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	Not applicable	09.05.2023 and 24.07.2023
EudraCT	https://eudract.ema.europa.eu/	Not applicable	09.05.2023 and 24.07.2023
ICTRP	https://www.who.int/clinical-trials-registry-platform	Not applicable	09.05.2023 and 24.07.2023
EU CTR	https://www.clinicaltrialsregister.eu/	Not applicable	09.05.2023 and 24.07.2023
Clinical Data search portal EMA	https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation	Not applicable	09.05.2023 and 24.07.2023

H.1.3.3 Health technology assessment database

To complement the electronic database searches for the SLR, additional searches were conducted in the health technology assessment (HTA) database provided in Table 73.

Table 73 HTA databases included in the literature search

Source name	Location/source	Search strategy	Date of search
INAHTA	https://database.inahta.org/	Not applicable	09.05.2023 and 24.07.2023

Abbreviations: HTA = health technology assessment; INAHTA = International Network of Agencies for Health Technology Assessment.

H.1.3.4 Conference proceedings

In addition, abstracts from the relevant congress websites provided in Table 74 (in agreement with Daiichi Sankyo Europe (DSE)) published in the past two years were searched to identify relevant studies.

Table 74 Conference material included in the literature search

Confer-ence	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	http://www.asco.org/	Electronic search	Not applicable	09.05.2023 and 24.07.2023
ASH	http://www.hematol-ogy.org/	Electronic search	Not applicable	09.05.2023 and 24.07.2023
EHA	https://ehaweb.org/	Electronic search	Not applicable	09.05.2023 and 24.07.2023
ESMO	http://www.esmo.org/	Electronic search	Not applicable	09.05.2023 and 24.07.2023
ISPOR	http://www.ispor.org/	Electronic search	Not applicable	09.05.2023 and 24.07.2023
ELN	https://www.leuke-mia-net.org/	Electronic search	Not applicable	09.05.2023 and 24.07.2023

H.1.4 Search strategies

The clinical SLR consists of a primary search conducted on May 9th, 2023, and an updated search conducted on July 24th, 2023. The updated search included azacitidine, which was not included in the primary search.

As recommended by various HTA agencies such as NICE (79), SMC (80), G-BA (81) and for comprehensiveness of the data collection, search strategies were developed through the combination of free text words, indexing terms (e.g., medical subject headings [MeSH] terms for Medline and Emtree terms for Embase) and by using Boolean terms (e.g. 'and', 'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the inclusion/exclusion criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax and presented in As recommended by various HTA agencies such as NICE (79), SMC (80), G-BA (81) and for comprehensiveness of the data collection, search strategies were developed through the combination of free text words, indexing terms (e.g., medical subject headings [MeSH] terms for Medline and Emtree terms for Embase) and by using Boolean terms (e.g. 'and', 'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the inclusion/exclusion criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax and presented in Table 75 to Table 79. The searches were run in OVID.

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. The clinical SLR searches were not limited by date or geographical location. The eligibility criteria are specified in Table 80.

H.1.4.1 Primary search

Table 75 Clinical SLR -Primary Search – Embase 1974 to 2023 Week 18

No.	Query	Results
#1	exp acute myeloid leukemia/	66,133
#2	((leukemia$ or leukaemia$] adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic]).ti,ab,kf.	148,828
#3	acute.ti,ab,kf.	2,023,567
#4	2 and 3	103,828
#5	(AML or ANLL].ti,ab,kf.	84,983
#6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,585
#7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	809
#8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or digulielmo$ or erythremic myelos$).ti,ab,kf.	5,949
#9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	155
#10	exp granulocytic sarcoma/	3,283
#11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	6,618
#12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	52
#13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	2,249
#14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	1,351
#15	exp secondary acute myeloid leukemia/	1,746
#16	(sAML or AML-MRC or tAML).ti,ab,kf.	1,705
#17	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	161,516
#18	CD135 antigen/	10,800
#19	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	17,164
#20	18 or 19	19,519
#21	cytarabine/	68,819
#22	(alcysten or alexan or ara C or ara-cell or arabinocytosil or arabinofuranosyl cytoside or arabinofuranosyl cytosine or arabinofuranosylcytosine or arabinoside c or arabinoside cytosine or arabinosine cytosine or arabinosyl cytosine or arabinosylcytosine or arabitin or aracytidine or aracytin or aracytine or beta ara c or citabion or citaloxan or citarabina or citarabine or cyclocide or cylocide or cystosine arabinoside or cytarabide or cytarabin or cytarabine or cytarabinoside cytarbine cytarine cytidine arabinoside cytoarabine cytosa u cytosar or cytosar 4 or cytosar u or cytosin arabinoside or cytosine arabinase or cytosine arabinofuranoside or cytosine arabinonucleoside or cytosine arabinose or cytosine arabinoside or cytosine arabinosine or cytosine beta arabinofuranoside or cytosine beta arabinoside or cytosine beta d arabinofuranoside or cytovis or depocyt or depocyte or dtc 101 or dtc101 or iretin or laracit or novumtrax or	72,401

No.	Query	Results
	nsc 63878 or nsc63878 or tarabine or u 19920 a or u 19920a or u19920a or udicil or 147-94-4 or 69-74-9).ti,ab,kf,rn.	
#23	daunorubicin/	30,853
#24	(cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or dauno rubidomycin or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicin or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or duanomycin or duanorubicin or fi 6339 or fi6339 or maxidauno or "ndc 0082 4155" or ndc 0082-4155 or "ndc 00824155" or ndc0082 4155 or ndc0082-4155 or ndc00824155 or nsc 82 151 or nsc 82151 or nsc82151 or rp 13057 or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or rubomycin c or rubomycine c or trixilem or trixilem ru or 12707-28-7 or 20830-81-3 or 23541-50-6 or 371770-68-2).ti,ab,kf,rn.	32,349
#25	idarubicin/	12,357
#26	(damycin or idamycin or idaralem or idarubicin or idarubicina or idarubicine or imi 30 or imi30 or nsc 256439 or nsc256439 or zacorist or zavedos or 57852-57-0 or 58957-92-9).ti,ab,kf,rn.	12,651
#27	mitoxantrone/	25,621
#28	(cl 232,315 or cl 232315 or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxantrone or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or now 85 34 or now 8534 or now8534 or nsc 279836 or nsc 301739 or nsc 301739d or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova or 65271-80-9 or 70476-82-3).ti,ab,kf,rn.	26,430
#29	etoposide/	99,664
#30	(bio 121 or bio121 or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopoextra or etopol or etopos or etoposid or etoposide or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213 or 33419-42-0 or 433304-61-1).ti,ab,kf,rn.	105,612
#31	fludarabine/	33,889
#32	(fludarabine or 2 fluoro 9 beta d arabinofuranosyladenine or 2 fluoroadenine 9 arabinoside or 2 fluoroadenine 9beta d arabinofuranoside or 2 fluoroadenine arabinofuranoside or 2 fluoroadenine arabinoside or 2 fluoroara a or 2 fluorovidarabine or 9 arabinofuranosyl 2 fluoroadenine or 9 beta arabinofuranosyl 2 fluoroadenine or 9 beta d arabinofuranosyl 2 fluoroadenine or 9 beta dextro arabinofuranosyl 2 fluoroadenine or 9beta arabinofuranosyl 2 fluoroadenine or 9beta d arabinofuranosyl 2 fluoroadenine or 9beta dextro arabinofuranosyl 2 fluoroadenine or adenine,9beta dextro arabinofuranosyl 2 fluoro or arabinofuranosyl 2 fluoroadenine or arabinosyl 2 fluoroadenine or f ara A or vidarabine,2 fluoro or 21679-1-1).ti,ab,kf,rn.	35,382
#33	amsaCrine/	4,112
#34	(amsaCrine or aCridinylanisidide or aCridinylmethanesulfonyl anisidide or aCridinylmethanesulfonylanisidide or aids-001997 or aids001997 or	4,888

No.	Query	Results
	amekrin or amerkin or AMSA or amsaCrina or amsaCrinum or amsakrin or amsidine or amsidyl or amsine or "brn 0500176" or ci 880 or ci-880 or ci880 or lamasine or m amsa or mamsa or meta-amsaCrine or nsc 141549 or nsc 156303 or nsc 2499 or nsc 249992 or nsc141549 or nsc156303 or nsc2499 or nsc249992 or sn 11841 or sn 21429 or sn-11841 or sn11841 or 51264-14-3 or 54301-15-4).ti,ab,kf,rn.	
#35	crenolanib/	693
#36	("aro 002" or "aro 002 26" or aro 002-26 or aro002 or aro002 26 or aro002-26 or cp 868596 or cp 868596 26 or cp868596 or cp868596 26 or crenolanib or 670220-88-9 or 670220-93-6).ti,ab,kf,rn.	705
#37	quizartinib/	1,493
#38	(quizartinib or "ac 010220" or ac 220 or ac010220 or ac220 or vanflyta or 1132827-21-4 or 950769-58-1).ti,ab,kf,rn.	1,562
#39	gilteritinib/	1,264
#40	(gilteritinib or asp 2215 or asp2215 or xospata or 1254053-43-4 or 1254053-84-3).ti,ab,kf,rn.	1,319
#41	midostaurin/	3,484
#42	(midostaurin or midostaurine or cgp 41251 or cgp41251 or pkc 412 or pkc412 or rydapt or 120685-11-2).ti,ab,kf,rn.	3,666
#43	or/21-42	215,812
#44	exp randomized controlled trial/	784,029
#45	"randomized controlled trial (topic)"/	259,038
#46	exp randomization/	99,309
#47	Double blind procedure/	209,899
#48	Single blind procedure/	51,621
#49	crossover procedure/	75,044
#50	placebo/	402,346
#51	exp clinical trial/	1,840,472
#52	double blind$.ti,ab,kw.	244,985
#53	single blind$.ti,ab,kw.	31,640
#54	(cross over or crossover).ti,ab,kw.	124,324
#55	(clinical adj3 trial$).ti,ab,kw.	713,567
#56	"randomi?ed controlled trial$".ti,ab,kw.	334,365
#57	RCT.ti,ab,kw.	55,595
#58	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab,kw.	284,525
#59	placebo$.ti,ab,kw.	367,859
#60	(random$ adj2 allocat$).ti,ab,kw.	54,537
#61	open label.ti,ab,kw.	108,547

No.	Query	Results
#62	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab,kw.	17,422
#63	Prospective Study/	872,618
#64	(single-arm adj3 trial$).ti,ab,kw.	6,937
#65	or/44-64	3,491,552
#66	17 and 20 and 43 and 65	1,955
#67	clinical study/	162,952
#68	case control study/	205,376
#69	longitudinal study/	192,845
#70	retrospective study/	1,459,428
#71	(cohort adj2 stud$).ti,ab,kw.	513,918
#72	cohort analysis/	1,029,032
#73	(Case control adj2 stud$).ti,ab,kw.	175,082
#74	(observational adj2 stud$).ti,ab,kw.	305,052
#75	(cross sectional adj2 stud$).ti,ab,kw.	390,971
#76	(follow up adj2 stud$).ti,ab,kw.	94,984
#77	(real world adj3 (evidence or data$)).ti,ab,kw.	34,369
#78	exp data base/	551,540
#79	exp observational study/	326,275
#80	exp register/	191,538
#81	exp electronic health record/	39,120
#82	exp electronic medical record/	77,855
#83	exp "medical record review"/	166,711
#84	((health or medical) adj3 (record$ or review$)).ti,ab,kw.	350,629
#85	exp health survey/	266,261
#86	exp medical record/	325,247
#87	(chart adj3 (review$ or study or studies)).ti,ab,kw.	117,229
#88	or/67-87	4,531,476
#89	17 and 20 and 43 and 88	1,075
#90	"systematic review"/	432,733
#91	meta analysis/	291,335
#92	(meta analy* or metanaly* or metaanaly*).ti,ab.	355,508
#93	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	436,562
#94	(search strategy or search Criteria or systematic search or study selection or data extraction).ab.	100,266

No.	Query	Results
#95	(search* adj4 literature).ab.	124,803
#96	(MEDLINE or pubmed or cochrane or embase).ab.	429,469
#97	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	7,046
#98	or/90-97	896,027
#99	17 and 20 and 43 and 98	118
#100	66 or 89 or 99	2,590
#101	exp animal/	30,583,707
#102	exp human/	25,412,039
#103	101 not (101 and 102)	5,171,668
#104	100 not 103	2,548
#105	case report/	2,895,219
#106	editorial/	742,480
#107	(editorial or note).pt.	1,711,005
#108	or/105-107	4,565,271
#109	104 not 108	2,386
#110	limit 109 to conference abstract	1,303
#111	limit 110 to yr="2020 -Current"	426
#112	109 not 110	1,083
#113	112 or 111	1,509

Table 76 Clinical SLR – Primary Search – OVID MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to May 08, 2023

No.	Query	Results
#1	exp leukemia, myeloid, acute/	63,871
#2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kf.	99,379
#3	acute.ti,ab,kf.	1,425,762
#4	2 and 3	64,643
#5	(AML or ANLL).ti,ab,kf.	41,601
#6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,670
#7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	517
#8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or digulielmo$ or erythremic myelos$).ti,ab,kf.	5,563
#9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	98

No.	Query	Results
#10	exp Sarcoma, Myeloid/	1,331
#11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	3,399
#12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	38
#13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	1,895
#14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	794
#15	(sAML or AML-MRC or tAML).ti,ab,kf.	544
#16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	105,017
#17	exp fms-Like Tyrosine Kinase 3/	3,406
#18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	7,573
#19	17 or 18	7,931
#20	cytarabine/	15,449
#21	(alcysten or alexan or ara C or ara-cell or arabinocytosil or arabinofuranosyl cytoside or arabinofuranosyl cytosine or arabinofuranosylcytosine or arabinoside c or arabinoside cytosine or arabinosine cytosine or arabinosyl cytosine or arabinosylcytosine or arabitin or aracytidine or aracytin or aracytine or beta ara c or citabion or citaloxan or citarabina or citarabine or cyclocide or cylocide or cystosine arabinoside or cytarabide or cytarabin or cytarabine or cytarabinoside cytarbine cytarine cytidine arabinoside cytoarabine cytosa u cytosar or cytosar 4 or cytosar u or cytosin arabinoside or cytosine arabinase or cytosine arabinofuranoside or cytosine arabinonucleoside or cytosine arabinose or cytosine arabinoside or cytosine arabinosine or cytosine beta arabinofuranoside or cytosine beta arabinoside or cytosine beta d arabinofuranoside or cytovis or depocyt or depocyte or dtc 101 or dtc101 or iretin or laracit or novumtrax or nsc 63878 or nsc63878 or tarabine or u 19920 a or u 19920a or u19920a or udicil or 147-94-4 or 69-74-9).ti,ab,kf.	15,878
#22	daunorubicin/	8,145
#23	(cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or dauno rubidomycin or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicin or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or duanomycin or duanorubicin or fi 6339 or fi6339 or maxidauno or "ndc 0082 4155" or ndc 0082-4155 or "ndc 00824155" or ndc0082 4155 or ndc0082-4155 or ndc00824155 or nsc 82 151 or nsc 82151 or nsc82151 or rp 13057 or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or rubomycin c or rubomycine c or trixilem or trixilem ru or 12707-28-7 or 20830-81-3 or 23541-50-6 or 371770-68-2).ti,ab,kf.	7,757
#24	idarubicin/	1,782
#25	(damycin or idamycin or idaralem or idarubicin or idarubicina or idarubicine or imi 30 or imi30 or nsc 256439 or nsc256439 or zacorist or zavedos or 57852-57-0 or 58957-92-9).ti,ab,kf.	1,920
#26	mitoxantrone/	4,411

No.	Query	Results
#27	(cl 232,315 or cl 232315 or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxantrone or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or now 85 34 or now 8534 or now8534 or nsc 279836 or nsc 301739 or nsc 301739d or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova or 65271-80-9 or 70476-82-3).ti,ab,kf.	5,850
#28	etoposide/	17,720
#29	(bio 121 or bio121 or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopoextra or etopol or etopos or etoposid or etoposide or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213 or 33419-42-0 or 433304-61-1).ti,ab,kf.	25,778
#30	(fludarabine or 2 fluoro 9 beta d arabinofuranosyladenine or 2 fluoroadenine 9 arabinoside or 2 fluoroadenine 9beta d arabinofuranoside or 2 fluoroadenine arabinofuranoside or 2 fluoroadenine arabinoside or 2 fluoroara a or 2 fluorovidarabine or 9 arabinofuranosyl 2 fluoroadenine or 9 beta arabinofuranosyl 2 fluoroadenine or 9 beta d arabinofuranosyl 2 fluoroadenine or 9 beta dextro arabinofuranosyl 2 fluoroadenine or 9beta arabinofuranosyl 2 fluoroadenine or 9beta d arabinofuranosyl 2 fluoroadenine or 9beta dextro arabinofuranosyl 2 fluoroadenine or adenine,9beta dextro arabinofuranosyl 2 fluoro or arabinofuranosyl 2 fluoroadenine or arabinosyl 2 fluoroadenine or f ara A or vidarabine,2 fluoro or 21679-1-1).ti,ab,kf.	6,043
#31	amsaCrine/	1,177
#32	(amsaCrine or aCridinylanisidide or aCridinylmethanesulfonyl anisidide or aCridinylmethanesulfonylanisidide or aids-001997 or aids001997 or amekrin or amerkin or AMSA or amsaCrina or amsaCrinum or amsakrin or amsidine or amsidyl or amsine or "brn 0500176" or ci 880 or ci-880 or ci880 or lamasine or m amsa or mamsa or meta-amsaCrine or nsc 141549 or nsc 156303 or nsc 2499 or nsc 249992 or nsc141549 or nsc156303 or nsc2499 or nsc249992 or sn 11841 or sn 21429 or sn-11841 or sn11841 or 51264-14-3 or 54301-15-4).ti,ab,kf.	1,763
#33	("aro 002" or "aro 002 26" or aro 002-26 or aro002 or aro002 26 or aro002-26 or cp 868596 or cp 868596 26 or cp868596 or cp868596 26 or crenolanib or 670220-88-9 or 670220-93-6).ti,ab,kf.	105
#34	(quizartinib or "ac 010220" or ac 220 or ac010220 or ac220 or vanflyta or 1132827-21-4 or 950769-58-1).ti,ab,kf.	285
#35	(gilteritinib or asp 2215 or asp2215 or xospata or 1254053-43-4 or 1254053-84-3).ti,ab,kf.	280
#36	(midostaurin or midostaurine or cgp 41251 or cgp41251 or pkc 412 or pkc412 or rydapt or 120685-11-2).ti,ab,kf.	781
#37	or/20-36	69,595
#38	exp Randomized Controlled Trials as Topic/	165,773
#39	exp randomized controlled trial/	593,864

No.	Query	Results
#40	random allocation/	106,927
#41	Double-Blind Method/	175,092
#42	Single-Blind Method/	32,687
#43	placebos/	35,926
#44	exp clinical trial/	969,677
#45	(cross over or crossover).ti,ab,kw.	97,849
#46	(clinical adj3 trial$).ti,ab,kw.	484,655
#47	"randomi?ed controlled trial$".ti,ab,kw.	249,117
#48	RCT.ti,ab,kw.	32,399
#49	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab,kw.	198,637
#50	placebo$.ti,ab,kw.	246,628
#51	(random$ adj2 allocat$).ti,ab,kw.	43,359
#52	open label.ti,ab,kw.	54,342
#53	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab,kw.	11,215
#54	(single-arm adj3 trial$).ti,ab,kw.	3,289
#55	or/38-54	1,761,889
#56	16 and 19 and 37 and 55	265
#57	Case-Control Studies/	327,636
#58	Longitudinal Studies/	164,738
#59	Retrospective Studies/	1,115,346
#60	Cohort Studies/	327,969
#61	(cohort adj2 stud$).ti,ab,kw.	337,333
#62	(Case control adj2 stud$).ti,ab,kw.	131,455
#63	Observational Study/	141,432
#64	(observational adj2 stud$).ti,ab,kw.	189,534
#65	Cross-Sectional Studies/	465,477
#66	(cross sectional adj2 stud$).ti,ab,kw.	290,932
#67	Follow-Up Studies/	691,284
#68	(follow up adj2 stud$).ti,ab,kw.	69,004
#69	exp Electronic Health Records/	27,480
#70	exp Medical Records/	158,807
#71	((health or medical) adj3 (record$ or review$)).ti,ab,kw.	211,673
#72	(chart adj2 (review$ or study or studies)).ti,ab,kw.	53,852
#73	(real world adj3 (evidence or data$)).ti,ab,kw.	17,085

No.	Query	Results
#74	(database$ or data base$ or registr$).ti,ab,kw.	983,005
#75	exp registries/	116,823
#76	or/57-75	4,005,198
#77	16 and 19 and 37 and 76	125
#78	"Systematic Review"/	227,889
#79	Meta-Analysis/	180,540
#80	(meta analy* or metanaly* or metaanaly*).ti,ab.	268,302
#81	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	349,211
#82	(search strategy or search Criteria or systematic search or study selection or data extraction).ab.	80,757
#83	(search* adj4 literature).ab.	96,232
#84	(MEDLINE or pubmed or cochrane or embase).ab.	329,291
#85	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	3,770
#86	78 or 79 or 80 or 81 or 82 or 83 or 84 or 85	636,882
#87	16 and 19 and 37 and 86	21
#88	56 or 77 or 87	368
#89	animals/ not humans/	5,085,699
#90	Editorial/ or Historical Article/ or case reports/	3,335,008
#91	(case reports or historical article or editorial).pt.	3,335,008
#92	90 or 91	3,335,008
#93	88 not 89	365
#94	93 not 92	356

Table 77 Clinical SLR – Primary Search – EBM Reviews - Cochrane Central Register of Controlled Trials April 2023, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 2, 2023

No.	Query	Results
#1	exp leukemia, myeloid, acute/	1,956
#2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kw.	6,812
#3	acute.ti,ab,kw.	159,825
#4	2 and 3	5,319
#5	(AML or ANLL).ti,ab,kw.	4,875
#6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kw.	274
#7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kw.	9

No.	Query	Results
#8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or digug-lielmo$ or erythremic myelos$).ti,ab,kw.	13
#9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kw.	0
#10	exp Sarcoma, Myeloid/	1
#11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neo-plasm$)).ti,ab,kw.	110
#12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kw.	1
#13	(chloroma$ or granulocytic sarcoma$).ti,ab,kw.	24
#14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leuke-mia$ or natural killer cell leukaemia$ or natural killer lym-phoma$).ti,ab,kw.	8
#15	(sAML or AML-MRC or tAML).ti,ab,kw.	117
#16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	7,185
#17	exp fms-Like Tyrosine Kinase 3/	71
#18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kw.	721
#19	17 or 18	725
#20	cytarabine/	1,516
#21	(alcysten or alexan or ara C or ara-cell or arabinocytosil or arabino-furanosyl cytoside or arabinofuranosyl cytosine or arabinofuranosylcyto-sine or arabinoside c or arabinoside cytosine or arabinosine cytosine or arabinosyl cytosine or arabinosylcytosine or arabitin or aracytidine or aracytin or aracytine or beta ara c or citabion or citaloxan or citarabina or citarabine or cyclocide or cylocide or cystosine arabinoside or cytarabide or cytarabin or cytarabine or cytarabinoside cytarbine cytarine cytidine arabinoside cytoarabine cytosa u cytosar or cytosar 4 or cytosar u or cy-tosin arabinoside or cytosine arabinase or cytosine arabinofuranoside or cytosine arabinonucleoside or cytosine arabinose or cytosine arabinoside or cytosine arabinosine or cytosine beta arabinofuranoside or cytosine beta arabinoside or cytosine beta d arabinofuranoside or cytovis or depo-cyt or depocyte or dtc 101 or dtc101 or iretin or laracit or novumtrax or nsc 63878 or nsc63878 or tarabine or u 19920 a or u 19920a or u19920a or udicil or 147-94-4 or 69-74-9).ti,ab,kw.	3,173
#22	daunorubicin/	684
#23	(cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or dauno rubidomycin or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicin or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or duanomycin or duanorubicin or fi 6339 or fi6339 or maxidauno or "ndc 0082 4155" or ndc 0082-4155 or "ndc 00824155" or ndc0082 4155 or ndc0082-4155 or ndc00824155 or nsc 82 151 or nsc 82151 or nsc82151 or rp 13057 or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or rubomycin c or rubomycine c or trixilem or trixilem ru or 12707-28-7 or 20830-81-3 or 23541-50-6 or 371770-68-2).ti,ab,kw.	1,136
#24	idarubicin/	279

No.	Query	Results
#25	(damycin or idamycin or idaralem or idarubicin or idarubicina or idarubicine or imi 30 or imi30 or nsc 256439 or nsc256439 or zacorist or zavedos or 57852-57-0 or 58957-92-9).ti,ab,kw.	661
#26	mitoxantrone/	555
#27	(cl 232,315 or cl 232315 or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxantrone or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or now 85 34 or now 8534 or now8534 or nsc 279836 or nsc 301739 or nsc 301739d or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova or 65271-80-9 or 70476-82-3).ti,ab,kw.	1,352
#28	etoposide/	1,999
#29	(bio 121 or bio121 or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopoextra or etopol or etopos or etoposid or etoposide or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213 or 33419-42-0 or 433304-61-1).ti,ab,kw.	3,980
#30	(fludarabine or 2 fluoro 9 beta d arabinofuranosyladenine or 2 fluoroadenine 9 arabinoside or 2 fluoroadenine 9beta d arabinofuranoside or 2 fluoroadenine arabinofuranoside or 2 fluoroadenine arabinoside or 2 fluoroara a or 2 fluorovidarabine or 9 arabinofuranosyl 2 fluoroadenine or 9 beta arabinofuranosyl 2 fluoroadenine or 9 beta d arabinofuranosyl 2 fluoroadenine or 9 beta dextro arabinofuranosyl 2 fluoroadenine or 9beta arabinofuranosyl 2 fluoroadenine or 9beta d arabinofuranosyl 2 fluoroadenine or 9beta dextro arabinofuranosyl 2 fluoroadenine or adenine,9beta dextro arabinofuranosyl 2 fluoro or arabinofuranosyl 2 fluoroadenine or arabinosyl 2 fluoroadenine or f ara A or vidarabine,2 fluoro or 21679-1-1).ti,ab,kw.	1,488
#31	amsaCrine/	75
#32	(amsaCrine or aCridinylanisidide or aCridinylmethanesulfonyl anisidide or aCridinylmethanesulfonylanisidide or aids-001997 or aids001997 or amekrin or amerkin or AMSA or amsaCrina or amsaCrinum or amsakrin or amsidine or amsidyl or amsine or "brn 0500176" or ci 880 or ci-880 or ci880 or lamasine or m amsa or mamsa or meta-amsaCrine or nsc 141549 or nsc 156303 or nsc 2499 or nsc 249992 or nsc141549 or nsc156303 or nsc2499 or nsc249992 or sn 11841 or sn 21429 or sn-11841 or sn11841 or 51264-14-3 or 54301-15-4).ti,ab,kf.	206
#33	("aro 002" or "aro 002 26" or aro 002-26 or aro002 or aro002 26 or aro002-26 or cp 868596 or cp 868596 26 or cp868596 or cp868596 26 or crenolanib or 670220-88-9 or 670220-93-6).ti,ab,kw.	28
#34	(quizartinib or "ac 010220" or ac 220 or ac010220 or ac220 or vanflyta or 1132827-21-4 or 950769-58-1).ti,ab,kw.	81
#35	(gilteritinib or asp 2215 or asp2215 or xospata or 1254053-43-4 or 1254053-84-3).ti,ab,kw.	96
#36	(midostaurin or midostaurine or cgp 41251 or cgp41251 or pkc 412 or pkc412 or rydapt or 120685-11-2).ti,ab,kw.	125

No.	Query	Results
#37	or/20-36	9,961
#38	16 and 19 and 37	423
#39	remove duplicates from 38	416

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

H.1.4.2 Updated search

Table 78 Clinical SLR – Update – OVID MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to July 24, 2023

No.	Query	Results
#1	exp leukemia, myeloid, acute/	64,429
#2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kf.	100,327
#3	acute.ti,ab,kf.	1,441,860
#4	2 and 3	65,401
#5	(AML or ANLL).ti,ab,kf.	42,226
#6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,670
#7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	523
#8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or digug-lielmo$ or erythremic myelos$).ti,ab,kf.	5,579
#9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	99
#10	exp Sarcoma, Myeloid/	1,342
#11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	3,481
#12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	38
#13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	1,902
#14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	812
#15	(sAML or AML-MRC or tAML).ti,ab,kf.	553
#16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	105,995
#17	exp fms-Like Tyrosine Kinase 3/	3,453
#18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	7,685
#19	17 or 18	8,044
#20	azacitidine/	7,472

No.	Query	Results
#21	(azacitidine or 5 azacyd or azacitidin or azacytidine or cc 486 or cc486 or ladakamycin mylosar or ns 17 or ns17 or nsc 102816 or nsc102816 or onureg or u 18496 or u18496 or vidaza or wr 183027 or wr183027 or 320-67-2).ti,ab,kf.	5,832
#22	cytarabine/	15,499
#23	(alcysten or alexan or ara C or ara-cell or arabinocytosil or arabinofuranosyl cytoside or arabinofuranosyl cytosine or arabinofuranosylcytosine or arabinoside c or arabinoside cytosine or arabinosine cytosine or arabinosyl cytosine or arabinosylcytosine or arabitin or aracytidine or aracytin or aracytine or beta ara c or citabion or citaloxan or citarabina or citarabine or cyclocide or cylocide or cystosine arabinoside or cytarabide or cytarabin or cytarabine or cytarabinoside cytarbine cytarine cytidine arabinoside cytoarabine cytosa u cytosar or cytosar 4 or cytosar u or cytosin arabinoside or cytosine arabinase or cytosine arabinofuranoside or cytosine arabinonucleoside or cytosine arabinose or cytosine arabinoside or cytosine arabinosine or cytosine beta arabinofuranoside or cytosine beta arabinoside or cytosine beta d arabinofuranoside or cytovis or depocyt or depocyte or dtc 101 or dtc101 or iretin or laracit or novumtrax or nsc 63878 or nsc63878 or tarabine or u 19920 a or u 19920a or u19920a or udicil or 147-94-4 or 69-74-9).ti,ab,kf.	15,981
#24	daunorubicin/	8,157
#25	(cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or dauno rubidomycin or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicin or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or duanomycin or duanorubicin or fi 6339 or fi6339 or maxidauno or "ndc 0082 4155" or ndc 0082-4155 or "ndc 00824155" or ndc0082 4155 or ndc0082-4155 or ndc00824155 or nsc 82 151 or nsc 82151 or nsc82151 or rp 13057 or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or rubomycin c or rubomycine c or trixilem or trixilem ru or 12707-28-7 or 20830-81-3 or 23541-50-6 or 371770-68-2).ti,ab,kf.	7,789
#26	idarubicin/	1,789
#27	(damycin or idamycin or idaralem or idarubicin or idarubicina or idarubicine or imi 30 or imi30 or nsc 256439 or nsc256439 or zacorist or zavedos or 57852-57-0 or 58957-92-9).ti,ab,kf.	1,936
#28	mitoxantrone/	4,424
#29	(cl 232,315 or cl 232315 or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxantrone or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or now 85 34 or now 8534 or now8534 or nsc 279836 or nsc 301739 or nsc 301739d or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova or 65271-80-9 or 70476-82-3).ti,ab,kf.	5,870
#30	etoposide/	17,786
#31	(bio 121 or bio121 or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopoextra or etopol or etopos or etoposid or etoposide or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or	25,925

No.	Query	Results
	toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213 or 33419-42-0 or 433304-61-1).ti,ab,kf.	
#32	(fludarabine or 2 fluoro 9 beta d arabinofuranosyladenine or 2 fluoroadenine 9 arabinoside or 2 fluoroadenine 9beta d arabinofuranoside or 2 fluoroadenine arabinofuranoside or 2 fluoroadenine arabinoside or 2 fluoroara a or 2 fluorovidarabine or 9 arabinofuranosyl 2 fluoroadenine or 9 beta arabinofuranosyl 2 fluoroadenine or 9 beta d arabinofuranosyl 2 fluoroadenine or 9 beta dextro arabinofuranosyl 2 fluoroadenine or 9beta arabinofuranosyl 2 fluoroadenine or 9beta d arabinofuranosyl 2 fluoroadenine or 9beta dextro arabinofuranosyl 2 fluoroadenine or adenine,9beta dextro arabinofuranosyl 2 fluoro or arabinofuranosyl 2 fluoroadenine or arabinosyl 2 fluoroadenine or f ara A or vidarabine,2 fluoro or 21679-1-1).ti,ab,kf.	6,085
#33	amsacrine/	1,177
#34	(amsacrine or acridinylanisidide or acridinylmethanesulfonyl anisidide or acridinylmethanesulfonylanisidide or aids-001997 or aids001997 or amekrin or amerkin or AMSA or amsacrina or amsacrinum or amsakrin or amsidine or amsidyl or amsine or "brn 0500176" or ci 880 or ci-880 or ci880 or lamasine or m amsa or mamsa or meta-amsacrine or nsc 141549 or nsc 156303 or nsc 2499 or nsc 249992 or nsc141549 or nsc156303 or nsc2499 or nsc249992 or sn 11841 or sn 21429 or sn-11841 or sn11841 or 51264-14-3 or 54301-15-4).ti,ab,kf.	1,768
#35	("aro 002" or "aro 002 26" or aro 002-26 or aro002 or aro002 26 or aro002-26 or cp 868596 or cp 868596 26 or cp868596 or cp868596 26 or crenolanib or 670220-88-9 or 670220-93-6).ti,ab,kf.	108
#36	(quizartinib or "ac 010220" or ac 220 or ac010220 or ac220 or vanflyta or 1132827-21-4 or 950769-58-1).ti,ab,kf.	291
#37	(gilteritinib or asp 2215 or asp2215 or xospata or 1254053-43-4 or 1254053-84-3).ti,ab,kf.	302
#38	(midostaurin or midostaurine or cgp 41251 or cgp41251 or pkc 412 or pkc412 or rydapt or 120685-11-2).ti,ab,kf.	801
#39	or/20-21	9,797
#40	exp Randomized Controlled Trials as Topic/	167,075
#41	exp randomized controlled trial/	598,803
#42	random allocation/	106,948
#43	Double-Blind Method/	175,808
#44	Single-Blind Method/	32,840
#45	placebos/	35,930
#46	exp clinical trial/	975,617
#47	(cross over or crossover).ti,ab,kw.	98,761
#48	(clinical adj3 trial$).ti,ab,kw.	493,068
#49	"randomi?ed controlled trial$".ti,ab,kw.	254,394
#50	RCT.ti,ab,kw.	33,195

No.	Query	Results
#51	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab,kw.	200,385
#52	placebo$.ti,ab,kw.	248,867
#53	(random$ adj2 allocat$).ti,ab,kw.	43,996
#54	open label.ti,ab,kw.	55,282
#55	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab,kw.	11,507
#56	(single-arm adj3 trial$).ti,ab,kw.	3,410
#57	or/40-56	1,779,476
#58	16 and 19 and 39 and 57	40
#59	Case-Control Studies/	328,851
#60	Longitudinal Studies/	166,143
#61	Retrospective Studies/	1,134,026
#62	Cohort Studies/	330,774
#63	(cohort adj2 stud$).ti,ab,kw.	346,119
#64	(Case control adj2 stud$).ti,ab,kw.	133,095
#65	Observational Study/	144,401
#66	(observational adj2 stud$).ti,ab,kw.	194,408
#67	Cross-Sectional Studies/	473,281
#68	(cross sectional adj2 stud$).ti,ab,kw.	298,760
#69	Follow-Up Studies/	692,553
#70	(follow up adj2 stud$).ti,ab,kw.	69,674
#71	exp Electronic Health Records/	27,877
#72	exp Medical Records/	159,399
#73	((health or medical) adj3 (record$ or review$)).ti,ab,kw.	215,611
#74	(chart adj2 (review$ or study or studies)).ti,ab,kw.	54,662
#75	(real world adj3 (evidence or data$)).ti,ab,kw.	18,003
#76	(database$ or data base$ or registr$).ti,ab,kw.	1,006,781
#77	exp registries/	117,545
#78	or/59-77	4,066,128
#79	16 and 19 and 39 and 78	15
#80	"Systematic Review"/	234,204
#81	Meta-Analysis/	184,720
#82	(meta analy* or metanaly* or metaanaly*).ti,ab.	275,692
#83	((systematic or evidence) adj3 (review* or overview*)).ti,ab.	359,161

No.	Query	Results
#84	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	82,886
#85	(search* adj4 literature).ab.	98,596
#86	(medline or pubmed or cochrane or embase).ab.	338,210
#87	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	3,833
#88	80 or 81 or 82 or 83 or 84 or 85 or 86 or 87	651,992
#89	16 and 19 and 39 and 88	9
#90	58 or 79 or 89	53
#91	animals/ not humans/	5,107,621
#92	Editorial/ or Historical Article/ or case reports/	3,358,339
#93	(case reports or historical article or editorial).pt.	3,358,339
#94	92 or 93	3,358,339
#95	90 not 91	53
#96	95 not 94	51

Table 79 Clinical SLR – Updated - EBM Reviews - Cochrane Central Register of Controlled Trials April 2023, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to Jul 24, 2023

No.	Query	Results
#1	exp leukemia, myeloid, acute/	1,965
#2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kw.	6,849
#3	acute.ti,ab,kw.	161,668
#4	2 and 3	5,353
#5	(AML or ANLL).ti,ab,kw.	4,914
#6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kw.	274
#7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kw.	9
#8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or digug-lielmo$ or erythremic myelos$).ti,ab,kw.	13
#9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kw.	0
#10	exp Sarcoma, Myeloid/	1
#11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neo-plasm$)).ti,ab,kw.	111
#12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kw.	1
#13	(chloroma$ or granulocytic sarcoma$).ti,ab,kw.	24

No.	Query	Results
#14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kw.	8
#15	(sAML or AML-MRC or tAML).ti,ab,kw.	117
#16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	7,237
#17	exp fms-Like Tyrosine Kinase 3/	72
#18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kw.	727
#19	17 or 18	731
#20	azacitidine/	404
#21	(azacitidine or 5 azacyd or azacitidin or azacytidine or cc 486 or cc486 or ladakamycin mylosar or ns 17 or ns17 or nsc 102816 or nsc102816 or onureg or u 18496 or u18496 or vidaza or wr 183027 or wr183027 or 320-67-2).ti,ab,kw.	1,012
#22	cytarabine/	1,522
#23	(alcysten or alexan or ara C or ara-cell or arabinocytosil or arabinofuranosyl cytoside or arabinofuranosyl cytosine or arabinofuranosylcytosine or arabinoside c or arabinoside cytosine or arabinosine cytosine or arabinosyl cytosine or arabinosylcytosine or arabitin or aracytidine or aracytin or aracytine or beta ara c or citabion or citaloxan or citarabina or citarabine or cyclocide or cylocide or cystosine arabinoside or cytarabide or cytarabin or cytarabine or cytarabinoside cytarbine cytarine cytidine arabinoside cytoarabine cytosa u cytosar or cytosar 4 or cytosar u or cytosin arabinoside or cytosine arabinase or cytosine arabinofuranoside or cytosine arabinonucleoside or cytosine arabinose or cytosine arabinoside or cytosine arabinosine or cytosine beta arabinofuranoside or cytosine beta arabinoside or cytosine beta d arabinofuranoside or cytovis or depocyt or depocyte or dtc 101 or dtc101 or iretin or laracit or novumtrax or nsc 63878 or nsc63878 or tarabine or u 19920 a or u 19920a or u19920a or udicil or 147-94-4 or 69-74-9).ti,ab,kw.	3,194
#24	daunorubicin/	685
#25	(cerubidin or cerubidine or dannomycin or daunamycin or daunarubicin or dauno rubidomycin or daunobin or daunoblastin or daunoblastina or daunoblastine or daunoextra or daunomycin or daunomycine or daunorrubicina or daunorubicin or daunorubicine or daunorubidomycin or daunorubimycin or daunoxome or daurorubicin or duanomycin or duanorubicin or fi 6339 or fi6339 or maxidauno or "ndc 0082 4155" or ndc 0082-4155 or "ndc 00824155" or ndc0082 4155 or ndc0082-4155 or ndc00824155 or nsc 82 151 or nsc 82151 or nsc82151 or rp 13057 or rp13057 or rubidiomycin or rubidomycin or rubidomycine or rubilem or rubomycin c or rubomycine c or trixilem or trixilem ru or 12707-28-7 or 20830-81-3 or 23541-50-6 or 371770-68-2).ti,ab,kw.	1,140
#26	idarubicin/	279
#27	(damycin or idamycin or idaralem or idarubicin or idarubicina or idarubicine or imi 30 or imi30 or nsc 256439 or nsc256439 or zacorist or zavedos or 57852-57-0 or 58957-92-9).ti,ab,kw.	663
#28	mitoxantrone/	558

No.	Query	Results
#29	(cl 232,315 or cl 232315 or cl232,315 or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxantrone or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or now 85 34 or now 8534 or now8534 or nsc 279836 or nsc 301739 or nsc 301739d or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova or 65271-80-9 or 70476-82-3).ti,ab,kw.	1,357
#30	etoposide/	2,006
#31	(bio 121 or bio121 or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopoextra or etopol or etopos or etoposid or etoposide or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213 or 33419-42-0 or 433304-61-1).ti,ab,kw.	3,998
#32	(fludarabine or 2 fluoro 9 beta d arabinofuranosyladenine or 2 fluoroadenine 9 arabinoside or 2 fluoroadenine 9beta d arabinofuranoside or 2 fluoroadenine arabinofuranoside or 2 fluoroadenine arabinoside or 2 fluoroara a or 2 fluorovidarabine or 9 arabinofuranosyl 2 fluoroadenine or 9 beta arabinofuranosyl 2 fluoroadenine or 9 beta d arabinofuranosyl 2 fluoroadenine or 9 beta dextro arabinofuranosyl 2 fluoroadenine or 9beta arabinofuranosyl 2 fluoroadenine or 9beta d arabinofuranosyl 2 fluoroadenine or 9beta dextro arabinofuranosyl 2 fluoroadenine or adenine,9beta dextro arabinofuranosyl 2 fluoro or arabinofuranosyl 2 fluoroadenine or arabinosyl 2 fluoroadenine or f ara A or vidarabine,2 fluoro or 21679-1-1).ti,ab,kw.	1,497
#33	amsacrine/	75
#34	(amsacrine or acridinylanisidide or acridinylmethanesulfonyl anisidide or acridinylmethanesulfonylanisidide or aids-001997 or aids001997 or amekrin or amerkin or AMSA or amsacrina or amsacrinum or amsakrin or amsidine or amsidyl or amsine or "brn 0500176" or ci 880 or ci-880 or ci880 or lamasine or m amsa or mamsa or meta-amsacrine or nsc 141549 or nsc 156303 or nsc 2499 or nsc 249992 or nsc141549 or nsc156303 or nsc2499 or nsc249992 or sn 11841 or sn 21429 or sn-11841 or sn11841 or 51264-14-3 or 54301-15-4).ti,ab,kf.	207
#35	("aro 002" or "aro 002 26" or aro 002-26 or aro002 or aro002 26 or aro002-26 or cp 868596 or cp 868596 26 or cp868596 or cp868596 26 or crenolanib or 670220-88-9 or 670220-93-6).ti,ab,kw.	28
#36	(quizartinib or "ac 010220" or ac 220 or ac010220 or ac220 or vanflyta or 1132827-21-4 or 950769-58-1).ti,ab,kw.	82
#37	(gilteritinib or asp 2215 or asp2215 or xospata or 1254053-43-4 or 1254053-84-3).ti,ab,kw.	97
#38	(midostaurin or midostaurine or cgp 41251 or cgp41251 or pkc 412 or pkc412 or rydapt or 120685-11-2).ti,ab,kw.	126
#39	or/20-21	1,149
#40	16 and 19 and 39	81

Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials.

H.1.5 Systematic selection of studies

H.1.5.1 Eligibility criteria

Selection of studies for inclusion was determined using the population, intervention, comparator, outcome, and study design (PICOS) framework (76). Full-text articles in languages other than the English language were excluded. The inclusion and exclusion criteria of the clinical literature reviews are presented in Selection of studies for inclusion was determined using the population, intervention, comparator, outcome, and study design (PICOS) framework (76). Full-text articles in languages other than the English language were excluded. The inclusion and exclusion criteria of the clinical literature reviews are presented in Table 80.

Table 80 Inclusion and exclusion criteria used for assessment of studies (PICOS)

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, Local adaption
Population	Adults (≥18 years old) with untreated AML that is *FLT3+*	• Condition other than 1L AML • Paediatric patients (<18 years old) • Non-human	N/R
Intervention and comparators	• Quizartinib • Midostaurin • Gilteritinib • Crenolanib • Cytarabine • Daunorubincin • Idarubicin • Mitoxantrone • Etopside • Amsacrine • Fludarabine • Azacitidine*	Any treatments/therapies not listed in the inclusion criteria	N/R
Outcomes	• Rate and duration of response (e.g., CR, CRc, CRi, and CRh)** • Progression-free survival • Event-free survival • Morphological leukemia-free state • Overall survival • Relapse-free survival	Studies not providing data on the specific outcomes of interest	N/R

	• Time to response • Time to progression/treatment failure • Transplantation rate • AE rate (all grade, grade 3+, SAE)*** • Any AE leading to discontinuation		
Study design/publication type	• RCTs, including cross-over studies • Non-randomised studies: observational studies (prospective and retrospective cohort studies); case-placebo and single-arm studies • SLRs and NMAs involving these study types ****	• Case studies • Editorials • Notes • Comments • Dose-finding studies • Dose-comparison studies • Pharmacokinetic studies • Pharmacodynamic studies • Maximum tolerated dose studies • Preclinical and phase I studies	N/R
Restrictions	• Language: English only studies • Publication date: no limitations • Conference abstracts published after 2020 • Country: no limitations	• Non-English language studies • Conference abstracts prior to 2020	N/R

Abbreviations: AE = adverse event; AML = acute myeloid leukaemia; CR = complete remission; CRh = CR with partial haematologic recovery; CRi = complete remission with incomplete neutrophil or platelet recovery; CRc = composite complete remission (includes CR = CRi = and CRh); FLT3+ = FMS-like tyrosine kinase 3 positive; NMA = network meta-analysis; PICOS = population = intervention = comparator = outcome and study design; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review; 1L = 1L.
Notes: *Azacitidine was included after the primary search had been completed. It is therefore reported separately from the other interventions. The same PICOS criteria were applied in the updated search, with the addition of azacitidine. ** Complete remission includes endpoints such as complete remission rate, composite complete remission rate, number of participants achieving complete remission, number of participants achieving composite complete remissions. ***This includes endpoint such as the number of participants with treatment emergent AEs. ****SLRs were included at abstract review stage in order to search their reference lists for any missed studies and subsequently excluded during full-text review stage.

H.1.5.2 Study selection process

H.1.5.2.1 Global SLR

In both the primary and the updated search, the following study selection process was applied. All records identified through the searches were exported to EndNote®, a bibliographic management software. After excluding duplicates, based on the title and abstract, references were reviewed in DistillerSR® by two reviewers independently against the predetermined eligibility (inclusion/exclusion) criteria using the PICOS framework (Table 80). All publications where there was uncertainty, or any disagreement were resolved either through “reconciliation” (discussion between the two reviewers) or, through “arbitration” by a third independent reviewer.

References identified as potentially relevant through the title and abstract review were retained for full-text screening. Similarly, full-text publications underwent independent assessment by two reviewers. Any uncertainties or disagreements were resolved through a process of "reconciliation" or, if necessary, "arbitration". All articles included from the full-text review were retained for data extraction. All publications excluded after full text review were recorded along with the reason for exclusion.

Primary search

The primary search yielded a total of 3,099 publications that were screened for inclusion. This included a total of 2,281 references identified from electronic database searches on May 9, 2023, three from HTA databases, 506 conference entries, and 309 registry records.

From the 2,281 publications identified via the database searches, 617 duplicate references were removed; 1,418 references were excluded after screening titles and abstracts against the eligibility criteria, and 246 potentially relevant references were retrieved for full-text assessment.

From the 818 titles identified via other methods, 809 references were excluded after screening titles and abstracts against the eligibility criteria, and 9 potentially relevant references were retrieved for full-text assessment.

Of the total 255 publications reviewed during full-text screening, 36 publications (reporting on 24 studies) were included for data extraction. 7 out of these 24 studies were ongoing interventional trials, or the results have not yet been reported.

Updated search

The updated search yielded a total of 712 publications that were screened for inclusion. This included a total of 541 references identified from electronic database searches on July 24, 2023, fourteen from HTA databases, 154 conference entries, and 3 registry records.

From the 541 publications identified via the database searches, 323 duplicate references were removed; 178 references were excluded after screening titles and abstracts against the eligibility criteria, and 40 potentially relevant references were retrieved for full-text assessment.

From the 171 titles identified via other methods, 145 references were excluded after screening titles and abstracts against the eligibility criteria, and 26 potentially relevant references were retrieved for full-text assessment.

Of the 66 publications reviewed during full-text screening, two publications (reporting on one study) were included for data extraction. It should be noted that none of the 26 references included for full-text assessment via other methods were included for data extraction. Therefore, the number of additional records identified through other sources is 0 in Figure 44.

H.1.5.2.2 Local adaptation

To inform this submission for quizartinib in Denmark, the global SLR has been adapted to exclude all studies not relevant in a Danish setting. For this reason, only studies examining quizartinib or midostaurin vs. placebo are included. In addition, studies not finalised or not reporting results were excluded from the local adaptation. Based on these criteria, 8 publications reporting two studies from the original search were included in the Danish assessment. No publications from the updated search were included in the Danish assessment.

The study selection processes of both the global SLRs and the local adaptations are detailed in the PRISMA flow-charts presented in Figure 43 and Figure 44.

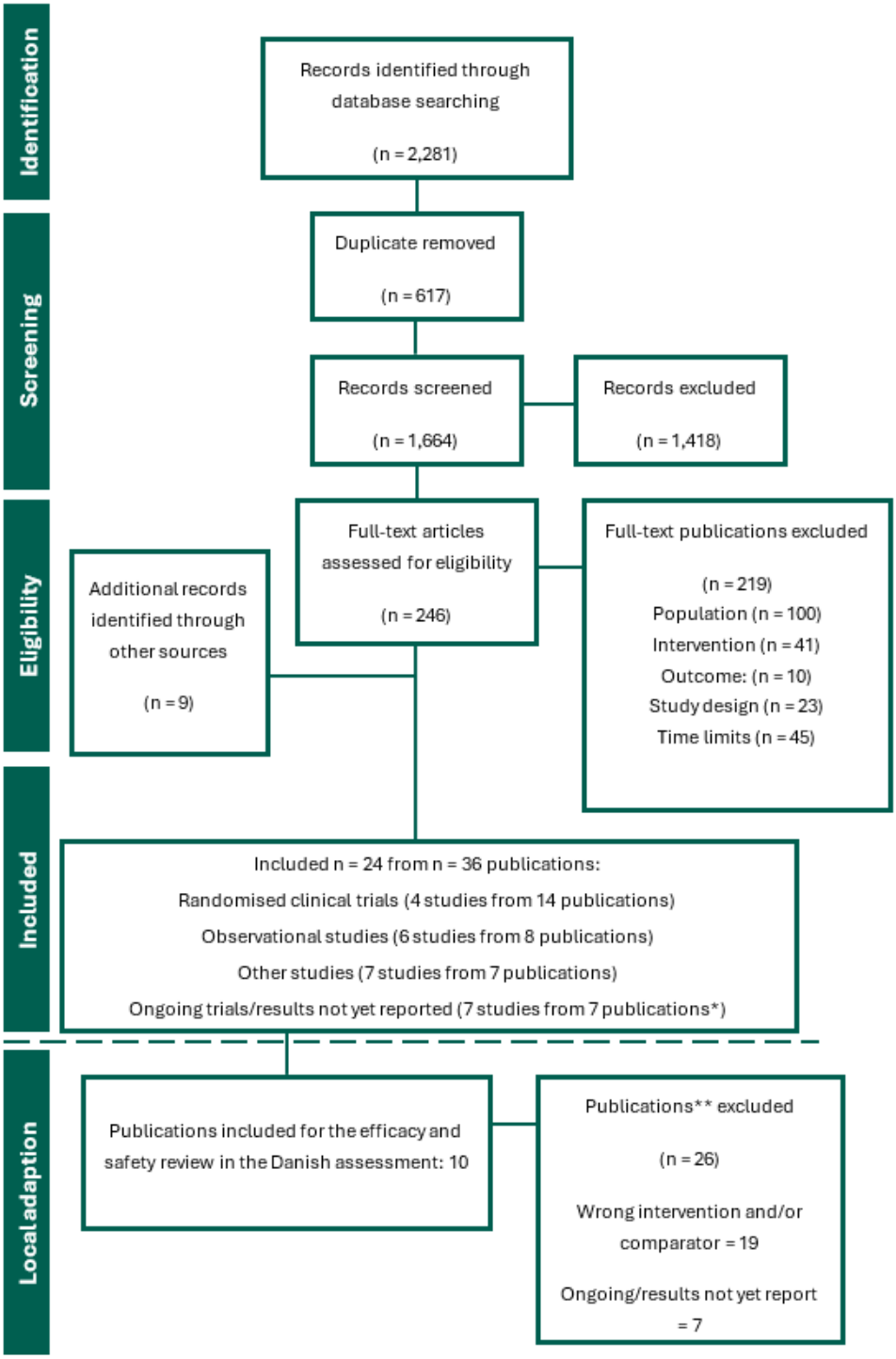


Figure 43 PRISMA flow-chart of the primary search

Notes: * Publications refer to web pages at ClinicalTrials.gov, which were included in the literature search (see appendix H.1.3.2). ** Publications include web pages at ClinicalTrials.gov from the ongoing trials/results not yet reported.

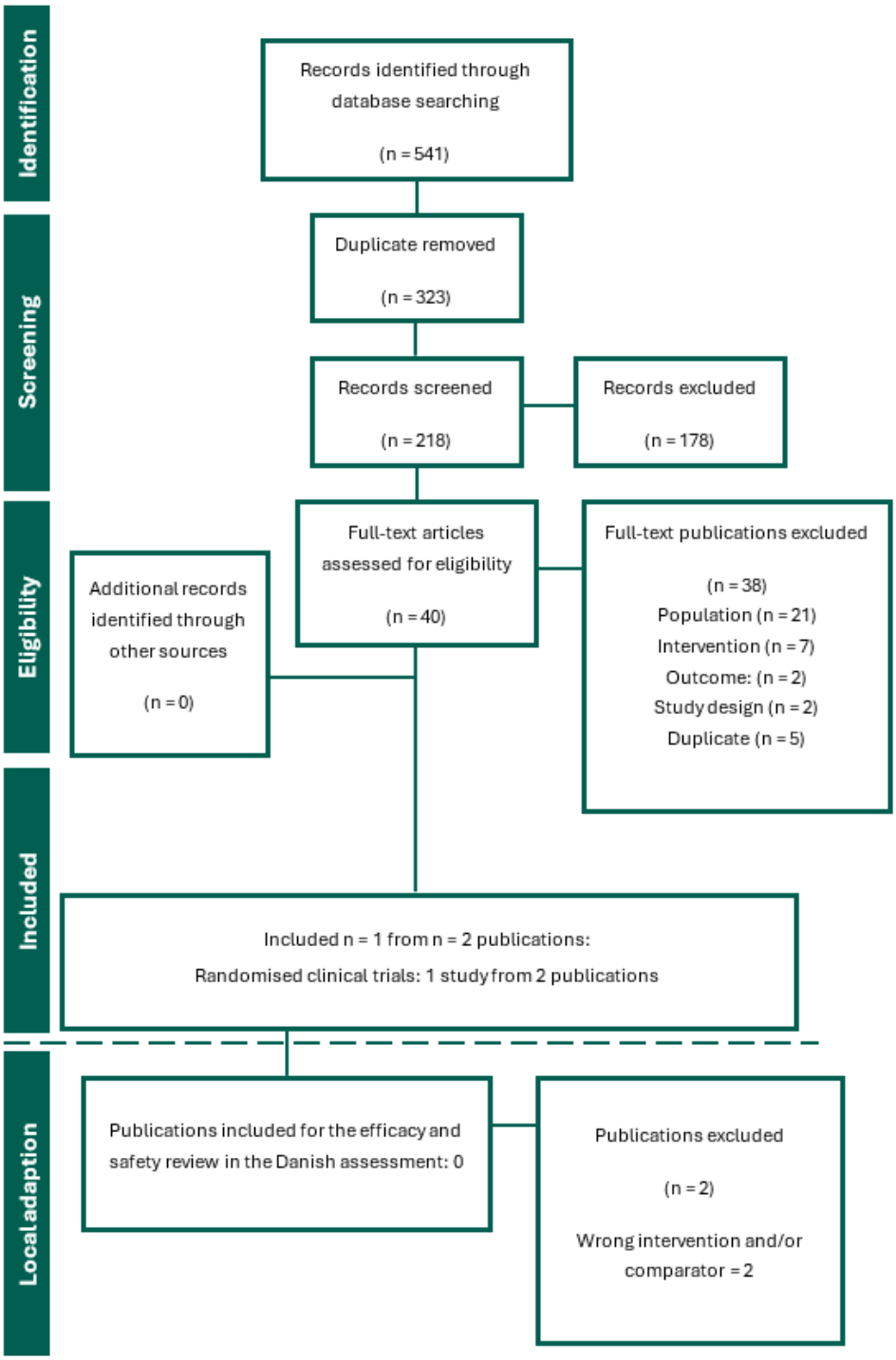


Figure 44 PRISMA flow-chart of the updated search

H.1.5.3 Summary of included studies

The primary search of the clinical SLR identified 24 studies described in 36 publications. Of these, seven were ongoing studies which did not report results. In total, the primary search identified 17 completed studies with results available. Additionally, 1 novel study was identified in the updated search. An overview of all included studies (n = 18) across both the primary and the updated search is provided in Table 81.

A summary of included studies in the local adaptation is presented in Table 82.

Table 81 Overview of study design for studies included in global analysis

Study/ID	Intervention	Comparator
Q-F (10)	Quizartinib + Chemotherapy (Cytarabine, Daunorubicin, Idarubicin)	Placebo + Chemotherapy
RATIFY (2)	Midostaurin + Chemo (Cytarabine, Daunorubicin, dexamethasone acetate)	Placebo + Chemotherapy
AMLSG 16-10 (82)	Midostaurin + Chemo (Cytarabine, Daunorubicin)	-
NCT03379727 (83)	Midostaurin + Chemo (Cytarabine, Daunorubicin)	-
(84)	Midostaurin	-
MDA-AML-2018-06 (85)	Midostaurin + Chemo	-
(86)	Midostaurin with conventional chemotherapy	-
PETHEMA AML (87)	Midostaurin + IC	-
(88)	Midostaurin + IC (Cytarabine, Daunorubicin)	-
(89)	Midostaurin + IC (Cytarabine, Daunorubicin)	-
(90)	Crenolanib with standard induction (cytarabine and daunorubicin/idarubicin)	-
(91)	Cytarabine with daunorubicin and sorafenib	Cytarabine with daunorubicin and placebo
UK AML 15 and UK AML 17 (92)	Conventional chemotherapy with lestaurtinib	Conventional chemotherapy with placebo
(93)	Induction: ICE; Consolidation: Idarubicin in association with High-Dose ARAC and HSCT	-
AML 96 (94)	Induction: Daunorubicin and cytarabine Consolidation: cytarabine and m-amsacrine	-
(95)	High-dose daunorubicin Standard-dose daunorubicin Idarubicin	-
(96)	Induction with chemotherapy and sorafenib	Induction with chemotherapy
QUAZAR AML-001 (97)	Azacitidine	Placebo

Two studies from 10 publications were included for the efficacy and safety review in the Danish assessment. An overview of the studies included in the local adaptation is provided in Table 82.

Table 82 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Q-F (NCT02668653) (10),(48),(49),(50).	N/A	RCT	Newly-diag-nosed FLT3–ITD+ AML	Quizartinib + SoC Placebo + SoC	OS	EFS, Overall AEs, TAEs
RATIFY (2), (3).(51).(53).(54).(54).	N/A	RCT	AML with FLT3 muta-tion	Midostaurin + SC Placebo + SC	OS	EFS, Overall AEs, TAEs

H.1.6 Excluded fulltext references

219 references were excluded because one of the following items was out of scope: population, intervention, study design, and outcomes or due to time limits. The list of the full text excluded reference is attached to this application as an excel file.

H.1.7 Quality assessment

The quality of each study included in the SLR was assessed in order to ensure that the conclusions and findings of this review are based on the best available evidence and that any potential sources of bias in the data were identified. The complete quality assessment of each included study was conducted adhering to NICE's HTA requirements.

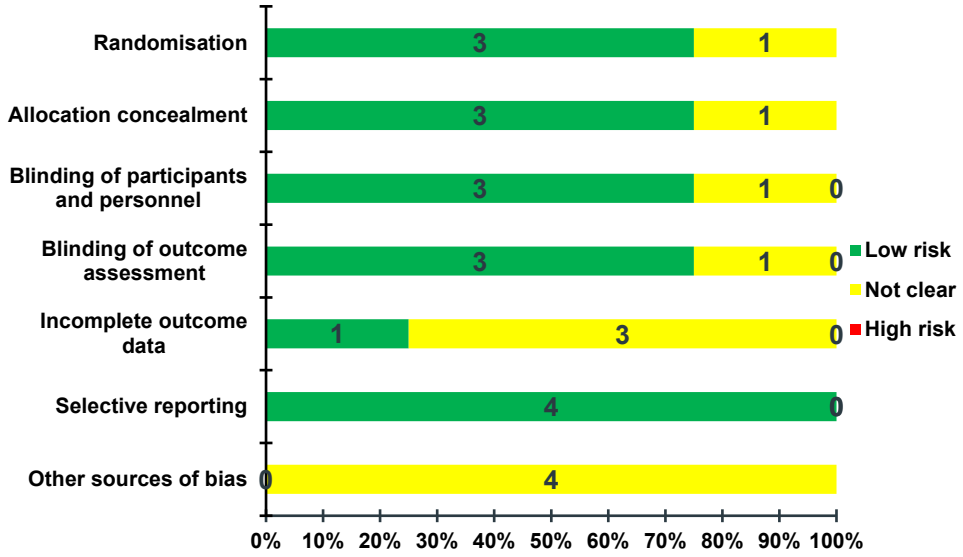
The quality of clinical RCTs retained for data extraction were assessed using the NICE checklist. The quality of non-RCTs retained for data extraction were assessed using the ROBINS-I assessment tool.

H.1.7.1 Quality assessment of the primary search

The risk-of-bias plot for the quality assessment of the four RCTs using the NICE checklist is provided in Figure 45. The risk of bias was assessed in seven distinct domains, with each answer leading to judgements of "low risk of bias", "not clear", or "high risk of bias.''. of the four RCTs were considered to have low risk in the domains "randomisation", "allocation concealment", "blinding of participants and personnel" and "blinding of outcome assessment", as they were randomised double-blind trials with detailed description of these processes. The fourth study (92) lacked information and was thus given a "not clear" assessment in these domains. Only one study provide information on "incomplete outcome data" and was thus the only study to be given a "low risk" assessment in this domain.

There was no indication for selective reporting in any of the studies , thus warranting a “low-risk” assessment for all. “Other sources of bias” could not be assessed leading to a “not-clear” assessment for all.

Figure 45. Quality of the included randomised trials in primary search as assessed using the NICE checklist

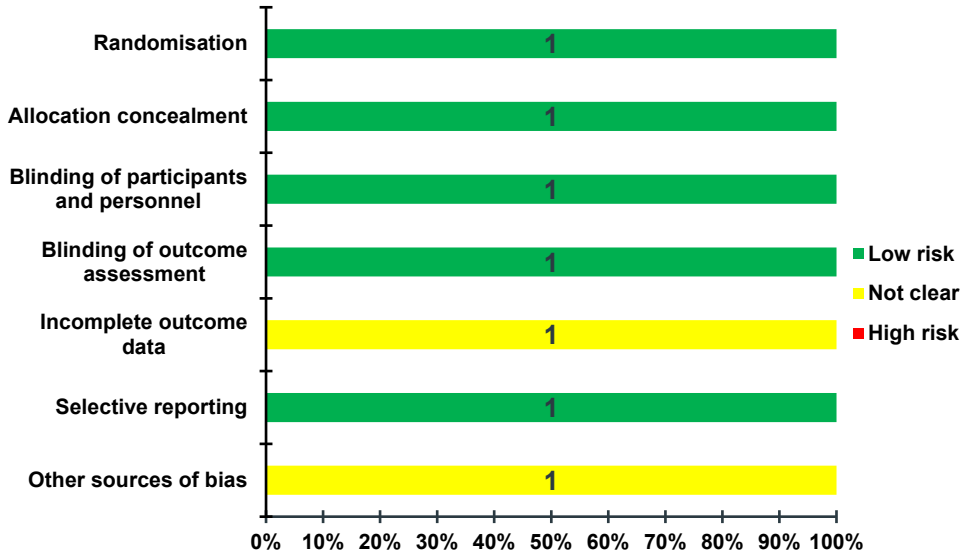


Abbreviations: NICE = National Institute for Health and Care Excellence.

H.1.7.2 Quality assessment of the updated search

The risk-of-bias plot for the quality assessment of the one RCT using the NICE checklist is provided in Figure 46. The risk of bias was assessed in seven distinct domains with each answer leading to judgements of “low risk of bias”, “not clear”, or “high risk of bias.’’ The study was considered low-risk in all domains other than “incomplete outcome data” and “other sources of bias” due to the information provided on blinding. A lack of information lead to a “not-clear” assessment for “incomplete outcome data” and “other sources of bias”.

Figure 46. Quality of the included randomised trials in azacitidine search as assessed using the NICE checklist



Abbreviations: NICE = National Institute for Health and Care Excellence.

H.1.8 Unpublished data

Not applicable. Unpublished data regarding the Q-F trial was main derived from the CSR and DS internal analysis.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

I.1.1.1 Objective

An SLR was conducted to support this HTA submission for quizartinib in newly diagnosed AML FLT3-ITD+ patients. The objective of this SLR was to identify relevant HRQoL evidence for patients with FLT3+ AML.

This SLR answers the following research questions:

- What are the utility/disutility weights of adults with AML that is FLT3+?
- What is the impact of FLT3+ AML first-line treatment on the HRQoL of these patients?

I.1.1.2 Methods

The SLR was conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (76), the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance (77) for undertaking reviews in health care, the PRISMA guidelines (78) and the methods for systematic reviews as specified by the NICE (79).

I.1.1.3 Information sources

I.1.1.3.1 Bibliographic databases

The OVID SP® platform was used to conduct the literature searches. The OVID SP® platform is a search platform that provides standardised access to a wide range of literature databases and is an accepted tool for use in a SLR. The databases in Table 83 were used to conduct the SLR searches, which are in line with recommendations from the Cochrane Collaboration (Higgins et al., 2019) and the NICE (National Institute for Health and Care Excellence (NICE), 2022) guidance. The HRQoL SLR search was conducted on 9th of May 2023.

Table 83 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to 2023 Week 18	09.05.2023
Medline	Ovid	1946 to March 27, 2023	09.05.2023
CENTRAL	Ovid	April 2023	09.05.2023
CDSR	Ovid	2005 to 2023 Week 18	09.05.2023

Database	Platform	Relevant period for the search	Date of search completion
NHS EED ®	Ovid	1st Quarter 2016	09.05.2023
HTA	Ovid	2011 to 4th Quarter 2016	09.05.2023
ScHARR	Ovid	2003 to 2023 Week 18	09.05.2023

Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; HTA = Health Technology Assessment; NHSEED = National Health Service Economic Evaluation Database; ScHARR = School of Health and Related Research

I.1.1.3.2 Trial registries

The search of trial registries is detailed in Appendix H.1.3.2. A list of included trial registries is provided in Table 84.

Table 84 Trial registries included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	Electronic search	09.05.2023
EudraCT	https://eudract.ema.europa.eu/	Electronic search	09.05.2023
ICTRP	https://www.who.int/clinical-trials-registry-platform	Electronic search	09.05.2023
EU CTR	https://www.clinicaltrialsregister.eu/	Electronic search	09.05.2023
Clinical Data search portal EMA	https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation	Electronic search	09.05.2023

Abbreviations: EMA = European Medicines Agency; EU CTR = European Union's Clinical Trials Register; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; ICTRP = International Clinical Trials Registry Platform.

I.1.1.3.3 HTA database

To complement the electronic database searches for the SLR, additional searches were conducted in the HTA database provided in Table 85.

Table 85 HTA databases included in the literature search

Source name	Location/source	Search strategy	Date of search
INAHTA		Electronic search	09.05.2023

Abbreviations: INAHTA = International Network of Agencies for Health Technology Assessment.

I.1.1.3.4 Conference proceedings

The search of conference proceedings is detailed in Appendix H.1.3.4H.1.3.2. A list of included conference material is provided in Table 86.

Table 86 Congress material included in the literature search

Congress	Location/source	Search strategy	Date of search
American Society of Clinical Oncology (ASCO)	http://www.asco.org/	Electronic search	09.05.2023
American Society of Haematology (ASH)	http://www.hematology.org/	Electronic search	09.05.2023
European Haematology Association (EHA)	https://ehaweb.org/	Electronic search	09.05.2023
European Society for Medical Oncology (ESMO)	http://www.esmo.org/	Electronic search	09.05.2023
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	http://www.ispor.org/	Electronic search	09.05.2023
European Leukaemia Net (ELN)	https://www.Leukaemia-net.org/	Electronic search	09.05.2023

I.1.1.3.5 Other

A hand-search of the reference lists of relevant studies, key SLRs, meta-analyses and network meta-analyses publications was also conducted.

I.1.1.4 Eligibility criteria

Selection of studies for inclusion was determined using the PICOS framework (76). Full-text articles in languages other than the English language were excluded. The inclusion and exclusion criteria of the HRQoL literature reviews are presented in Table 87.

Table 87 Eligibility criteria of HRQoL SLR

PICOS	Inclusion criteria	Exclusion criteria
Patient population	• Adults (≥18 years old) with AML that is FLT3+	• Condition other than AML • Paediatric patients (<18 years old) • Non-human
Interventions/comparator	• No limitations	• None
Outcomes	Studies reporting utilities and disutilities for the population of interest using any utility measure, including: • EQ-5D • EORTC QLQ-C30 • SF-36/12 • HUI • MRC/EORTC QLQ-LEU • MDASI-AML • FACT-G, • FACT-Leu	• Studies not providing data on the specific outcomes of interest

	• AML-QOL • Standard gamble	
Study design	• Studies reporting HRQoL/utility/disutility data SLRs involving these study types*	• Case studies • Editorials • Notes • Comments
Restrictions	• Language: English only studies • Publication date: no limitations • Conference abstracts published after 2020 • Country: no limitations	• Non-English language studies • Conference abstracts prior to 2020

I.1.1.5 Search strings

As recommended by various HTA agencies such as NICE (79), SMC (80), G-BA (81) and for comprehensiveness of the data collection, search strategies were developed through the combination of free text words, indexing terms (e.g. medical subject headings [MeSH] terms for Medline and Emtree terms for Embase] and by using Boolean terms (e.g. 'and', 'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the inclusion/exclusion criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax and presented in Table 75 - Table 90. The searches were run in OVID.

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. The HRQoL SLR searches were not limited by date or geographical location.

Table 88 Search strategy for Embase

#	Query	Results
1	exp acute myeloid leukemia/	66,133
2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kf.	148,828
3	acute.ti,ab,kf.	2,023,567
4	2 and 3	103,828
5	(AML or ANLL).ti,ab,kf.	84,983
6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,585
7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	809
8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or diguglielmo$ or erythremic myelos$).ti,ab,kf.	5,949

9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	155
10	exp granulocytic sarcoma/	3,283
11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	6,618
12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	52
13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	2,249
14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	1,351
15	exp secondary acute myeloid leukemia/	1,746
16	(sAML or AML-MRC or tAML).ti,ab,kf.	1,705
17	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	161,516
18	CD135 antigen/	10,800
19	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	17,164
20	18 or 19	19,519
21	exp socioeconomics/	1,298,899
22	exp "quality of life"/	643,511
23	(quality of life or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	600,486
24	((index adj3 wellbeing) or wellbeing or ((quality adj3 wellbeing) or well being) or qwb).ti,ab,kf.	173,700
25	(year$ adj4 (healthy life or equivalent or potential life or lost)).ti,ab,kf.	13,541
26	(utility score$ or disutilit$).ti,ab,kf.	4,565
27	((health* or validation or validate$ or elicit$ or elicitation or score$1 or scoring or value$ or evaluate$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status) adj3 utilit*).ti,ab,kf.	67,147
28	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	25,483
29	exp quality adjusted life year/	35,089
30	(qaly$ or qald$ or qale$ or qtime$ or daly$ or haly$ or yhl or hye or hyes or ypll or yhll).ti,ab,kw.	34,254
31	Health Status Indicators.ab,ti,kf.	928
32	(health adj2 (utilit$ or status)).ti,ab,kf.	110,964
33	(illness state$1 or health state$1).ti,ab,kf.	14,601
34	(hui or hui1 or hui2 or hui3).ti,ab,kf.	3,076
35	disutili$.ti,ab,kf.	1,236

36	Willingness To Pay/	2,737
37	willingness to pay.ab,ti,kw.	12,983
38	Standard Gamble/	81
39	(standard gamble$ or sg).ti,ab,kf.	21,092
40	(mapping$ or mapped or crosswalk$ or cross walk$).ti,ab,kf.	336,941
41	exp "European Quality of Life 5 Dimensions questionnaire"/	14,200
42	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or eu-roqol5d).ti,ab,kf.	29,896
43	exp Short Form 36/	48,789
44	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	50,058
45	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ab,ti,kf.	521
46	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ab,ti,kf.	70
47	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ab,ti,kf.	12,281
48	(sf6 or sf 6 or sf6d or sf 6d or short form 6 or short form 6d or shortform 6d or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,kf.	4,605
49	(The Functional Assessment of Cancer Therapy Leukemia or FACT leukemia or FACT-Leu).ti,ab,kf.	159
50	(The Functional Assessment of Cancer Therapy General or FACT General or FACT-G).ti,ab,kf.	2,327
51	("MDASI-AML/MDS" or MDASI-AML).ti,ab,kf.	9
52	("MD Anderson Symptom Inventory" or "Life Ingredient Profile" or LIP).ti,ab,kf.	51,184
53	(AML-QOL or Acute Myeloid Leukemia-Quality of Life).ti,ab,kf.	5
54	or/21-53	2,662,484
55	17 and 20 and 54	483
56	exp animal/	30,583,707
57	exp human/	25,412,039
58	56 not (56 and 57)	5,171,668
59	case report/	2,895,219
60	editorial/	742,480
61	(editorial or note).pt.	1,711,005
62	59 or 60 or 61	4,565,271
63	55 not 58	471
64	63 not 62	444
65	limit 64 to conference abstract	280

66	limit 65 to yr="2020 -Current"	89
67	64 not 65	164
68	66 or 67	253

Table 89 Search strategy for Ovid Medline Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations

#	Query	Results
1	exp leukemia, myeloid, acute/	63,871
2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kf.	99,379
3	acute.ti,ab,kf.	1,425,762
4	2 and 3	64,643
5	(AML or ANLL).ti,ab,kf.	41,601
6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,670
7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	517
8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or digug-lielmo$ or erythremic myelos$).ti,ab,kf.	5,563
9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	98
10	exp Sarcoma, Myeloid/	1,331
11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	3,399
12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	38
13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	1,895
14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	794
15	(sAML or AML-MRC or tAML).ti,ab,kf.	544
16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	105,017
17	exp fms-Like Tyrosine Kinase 3/	3,406
18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	7,573
19	17 or 18	7,931
20	exp "quality of life"/	265,230
21	(quality of life or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	373,572
22	Quality-Adjusted Life Years/	15,594
23	quality adjusted life.ti,ab,kf.	17,168

24	(qaly$ or qald$ or qale$ or qtime$ or daly$ or haly$ or yhl or hye or hyes or ypll or yhll).ti,ab,kf.	20,084
25	((index adj3 wellbeing) or wellbeing or ((quality adj3 wellbeing) or well being) or qwb).ti,ab,kf.	137,471
26	(year$ adj4 (healthy life or equivalent or potential life or lost)).ti,ab,kf.	9,525
27	((disability adjusted or health adjusted or quality adjusted) adj4 year$).ti,ab,kf.	22,083
28	(utility score$ or disutilit$).ti,ab,kf.	2,447
29	((health* or validation or validate$ or elicit$ or elicitation or score$1 or scoring or value$ or evaluate$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status) adj3 utilit*).ti,ab,kf.	42,262
30	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	15,713
31	Health Status Indicators.ab,ti,kf.	545
32	(health adj2 (utilit$ or status)).ti,ab,kf.	83,397
33	(illness state$1 or health state$1).ti,ab,kf.	8,268
34	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1,945
35	disutili$.ti,ab,kf.	612
36	willingness to pay.ab,ti,kw.	8,412
37	(standard gamble$ or sg).ti,ab,kf.	14,006
38	(mapping$ or mapped or crosswalk$ or cross walk$).ti,ab,kf.	274,858
39	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf.	16,243
40	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	30,403
41	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ab,ti,kf.	455
42	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ab,ti,kf.	39
43	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ab,ti,kf.	7,562
44	(sf6 or sf 6 or sf6d or sf 6d or short form 6 or short form 6d or shortform 6d or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,kf.	3,478
45	(The Functional Assessment of Cancer Therapy Leukemia or FACT leukemia or FACT-Leu).ti,ab,kf.	49

46	(The Functional Assessment of Cancer Therapy General or FACT General or FACT-G).ti,ab,kf.	1,153
47	("MDASI-AML/MDS" or MDASI-AML).ti,ab,kf.	2
48	("MD Anderson Symptom Inventory" or "Life Ingredient Profile" or LIP).ti,ab,kf.	42,985
49	(AML-QOL or Acute Myeloid Leukemia-Quality of Life).ti,ab,kf.	3
50	or/20-49	1,006,582
51	16 and 19 and 50	53
52	animals/ not humans/	5,085,699
53	Editorial/ or Historical Article/ or case reports/	3,335,008
54	(case reports or historical article or editorial).pt.	3,335,008
55	51 not 52	51
56	53 or 54	3,335,008
57	55 not 56	48

Table 90 Search strategy for EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database

#	Query	Results
1	exp leukemia, myeloid, acute/	1,956
2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kw.	6,903
3	acute.ti,ab,kw.	160,766
4	2 and 3	5,355
5	(AML or ANLL).ti,ab,kw.	4,880
6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kw.	274
7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kw.	9
8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or diguglielmo$ or erythremic myelos$).ti,ab,kw.	13
9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kw.	0
10	exp Sarcoma, Myeloid/	1
11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kw.	110
12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kw.	1
13	(chloroma$ or granulocytic sarcoma$).ti,ab,kw.	24

14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kw.	8
15	(sAML or AML-MRC or tAML).ti,ab,kw.	117
16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	7,221
17	(cd135 or FLT3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	719
18	exp fms-Like Tyrosine Kinase 3/	71
19	17 or 18	723
20	exp "quality of life"/	43,744
21	(quality of life or hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	139,160
22	Quality-Adjusted Life Years/	5,188
23	quality adjusted life.ti,ab,kw.	5,886
24	(qaly$ or qald$ or qale$ or qtime$ or daly$ or haly$ or yhl or hye or hyes or ypll or yhll).ti,ab,kw.	5,069
25	((index adj3 wellbeing) or wellbeing or ((quality adj3 wellbeing) or well being) or qwb).ti,ab,kw.	22,245
26	(year$ adj4 (healthy life or equivalent or potential life or lost)).ti,ab,kw.	873
27	((disability adjusted or health adjusted or quality adjusted) adj4 year$).ti,ab,kw.	6,150
28	(utility score$ or disutilit$).ti,ab,kw.	738
29	((health* or validation or validate$ or elicit$ or elicitation or score$1 or scoring or value$ or evaluate$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status) adj3 utilit*).ti,ab,kw.	7,489
30	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.	3,290
31	Health Status Indicators.ab,ti,kw.	48
32	(health adj2 (utilit$ or status)).ti,ab,kw.	15,318
33	(illness state$1 or health state$1).ti,ab,kw.	1,513
34	(hui or hui1 or hui2 or hui3).ti,ab,kw.	309
35	disutili$.ti,ab,kw.	107
36	willingness to pay.ab,ti,kw.	1,890
37	(standard gamble$ or sg).ti,ab,kw.	1,741
38	(mapping$ or mapped or crosswalk$ or cross walk$).ti,ab,kw.	5,259
39	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kw.	12,441

40	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	16,452
41	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ab,ti,kw.	101
42	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ab,ti,kw.	14
43	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ab,ti,kw.	3,544
44	(sf6 or sf 6 or sf6d or sf 6d or short form 6 or short form 6d or shortform 6d or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,kw.	553
45	(The Functional Assessment of Cancer Therapy Leukemia or FACT leukemia or FACT-Leu).ti,ab,kw.	63
46	(The Functional Assessment of Cancer Therapy General or FACT General or FACT-G).ti,ab,kw.	657
47	("MDASI-AML/MDS" or MDASI-AML).ti,ab,kw.	2
48	("MD Anderson Symptom Inventory" or "Life Ingredient Profile" or LIP).ti,ab,kw.	2,789
49	(AML-QOL or Acute Myeloid Leukemia-Quality of Life).ti,ab,kw.	0
50	or/20-49	191,340
51	16 and 19 and 50	36
52	animals/ not humans/	2,690
53	Editorial/ or Historical Article/ or case reports/	112
54	(case reports or historical article or editorial).pt.	3,370
55	51 not 52	36
56	53 or 54	3,378
57	55 not 56	36

I.1.1.6 Results

The PRISMA flow diagram of the HRQoL SLR is presented in Figure 47 below. In total 1,154 publications were screened for inclusion. This included a total of 337 references identified from electronic databases searches on the 9th of May 2023, (Medline®: 48; Embase®: 253; EBM reviews®: 36) and an additional 817 publications from trial registries and hand-searching of conference proceedings. No additional relevant studies were identified by cross-checking the references of six SLRs identified in the database searches.

From the 337 publications identified via database search, 18 duplicate references were removed; 274 references were excluded after screening titles and abstracts against the eligibility criteria and 45 potentially relevant references were retrieved for full-text assessment. Of these 45 publications, 8 (7 full text and 1 conference abstract) were included for data extraction.

From the 817 records identified from the other methods, 2 NICE appraisals were identified via the hand search and extracted. From the 10 studies included in the review, 1 was leveraged in the health economic model to derive the HRQOL of patients in HSCT states, namely NICE TA523.

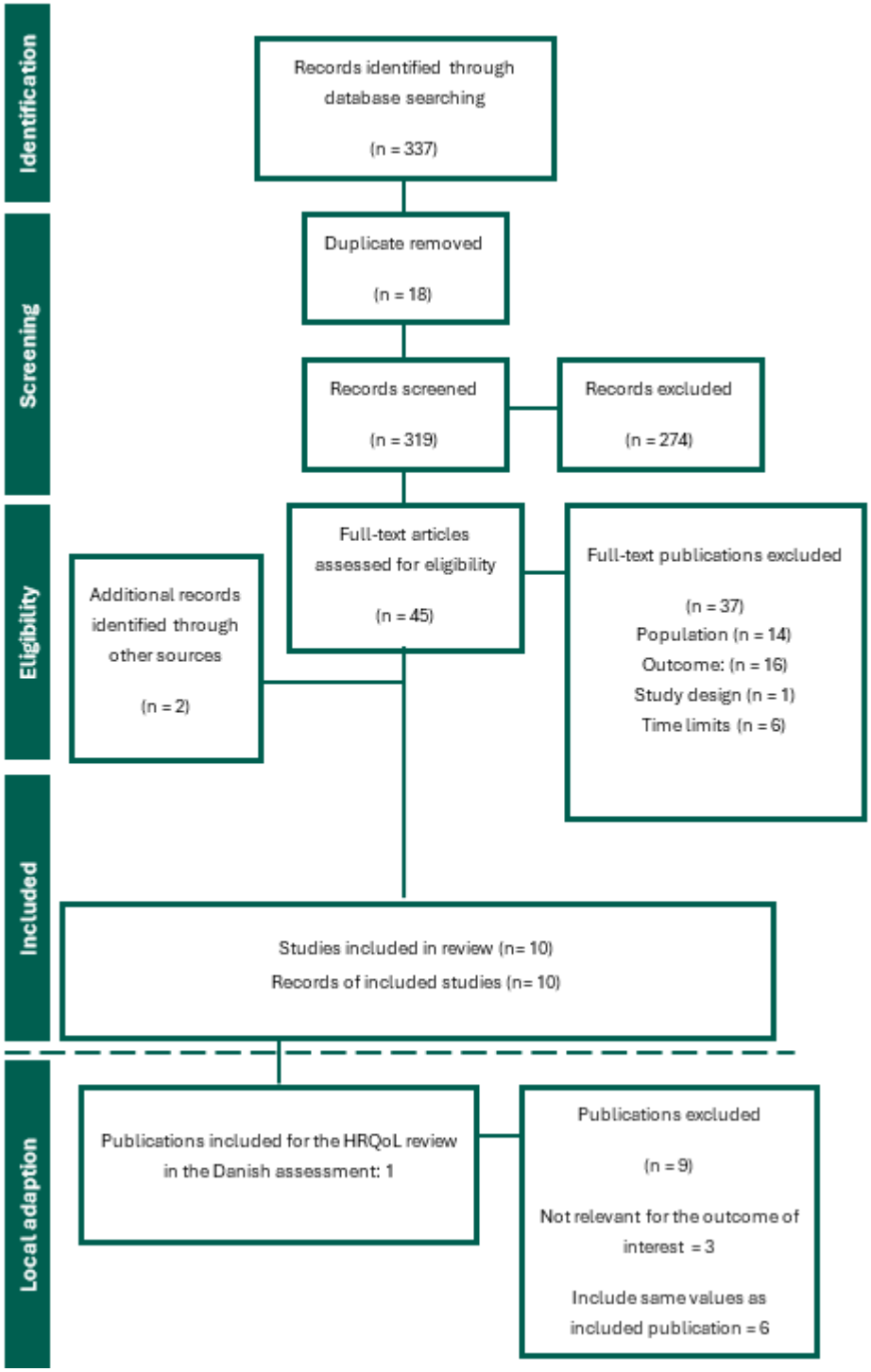


Figure 47 PRISMA flow diagram for HRQoL studies

A list of included studies is provided in Table 91.

Table 91 List of included studies in global SLR

Study reference	Trial ID (if applicable)	Population	Country of study	Study design
Tremblay 2018 (98)	NR	ND FLT3+ AML	UK	Cost-effectiveness analysis
NICE TA523 (31)	NA	ND FLT3+ AML	UK	Cost-effectiveness analysis
NICE TA642 (68)	NA	FLT3+ R/R AML	UK	Cost-effectiveness analysis
Ritchie 2023 (99)	NCT02421939	R/R FLT3+ AML	Multicentre, including patients in UK	Phase III, open label, RCT
Wang 2021 (100)	NCT02752035	ND FLT3+ AML patients who are ineligible to SC	Multicentre, including patients in UK	Phase III, open label, RCT
Horvath Walsh 2019 (26)	NR	FLT3+ AML	US	Observational study
Arenaza 2019 (101)	NCT00651261	ND FLT3+AML	Spain	Cost-effectiveness analysis
Tremblay 2020 (102)	NCT00651261	ND FLT3+ AML	France	Cost-effectiveness analysis
Stein 2019 (103)	NCT00651261	ND FLT3+ AML	US	Cost-effectiveness analysis
Pandya 2021 (104)	NCT02421939	R/R FLT3+ AML	US	Cost-effectiveness analysis

A list of publications excluded at the full-text review stage from the global SLR as well as reason for exclusion is provided in Table 92.

Table 92 Publications excluded at the full-text review stage from the HRQoL global SLR

No.	Publication	Exclusion reason
#1	Oral Azacitidine for Maintenance Treatment of Acute Myeloid Leukaemia After Induction Therapy: An Evidence Review Group Perspective of a NICE Single Technology Appraisal	Outcome
#2	The relationship between emotional well-being and understanding of prognosis in patients with acute myeloid leukemia (AML)	Population
#3	Safety profile and impact on survival of tyrosine kinase inhibitors versus conventional therapy in relapse or refractory FLT3 positive acute myeloid leukemia patients	Outcome
#4	Decision Analysis of Postremission Therapy in Cytogenetically Intermediate-Risk Acute Myeloid Leukemia: The Impact of FLT3 Internal Tandem Duplication, Nucleophosmin, and CCAAT/Enhancer Binding Protein Alpha	Population
#5	Health economic evidence for the use of molecular biomarker tests in hematological malignancies: A systematic review	Population

#6	Pharmacoeconomic considerations for acute myeloid leukemia pharmacotherapy	Study design
#7	PRELIMINARY RESULTS OF VEN-A-QUI STUDY: A PHASE 1-2 TRIAL TO ASSESS THE SAFETY AND EFFICACY OF THE COMBINATION OF AZACITIDINE OR LOW-DOSE CYTARABINE WITH VENETOCLAX AND QUIZARTINIB IN NEWLY DIAGNOSED	Population
#8	A phase 2, multicenter, randomized, doubleblind trial of maintenance therapy with FLT3 inhibitor gilteritinib (ASP2215) in patients with FLT3/ITD AML (GOSSAMER study)	Outcome
#9	Impact of treatment delay in acute myeloid leukemia revisited	Population
#10	Risk adapted therapeutic strategy in newly diagnosed acute myeloid leukemia: Refining the outcomes of ELN 2017 intermediate-risk patients	Population
#11	Allogeneic hematopoietic cell transplantation in patients <= 60 years with intermediate-risk acute myeloid leukemia in first remission-results of the randomized etal-1 trial	Population
#12	Symptoms and Impacts Reported By Patients with Acute Myeloid Leukemia (AML) in Remission Post-Stem Cell Transplant	Population
#13	Pain and opioid use in patients with FLT3 mutation-positive relapsed/refractory AML: A subanalysis of patient-reported outcomes from the admiral trial	Time limit
#14	Real world outcomes of liposomal daunorubicin and cytarabine versus 7+3 in patients with secondary acute myeloid leukemia	Population
#15	PCN306 ESTIMATION OF HEALTH STATE UTILITIES IN FLT3-MUTATED RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA	Time limit
#16	PCN336 PSYCHOMETRIC ANALYSIS OF PATIENT-REPORTED OUTCOME MEASURES IN FLT3-MUTATED RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA	Outcome
#17	PCN36 A SYSTEMATIC REVIEW OF THE HUMANISTIC BURDEN OF FLT3-MUTATED RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA	Outcome
#18	FLT3 inhibitors in acute myeloid leukaemia: assessment of clinical effectiveness, adverse events and future research-a systematic review and meta-analysis	Outcome
#19	Relationship between patient-reported outcomes and clinical out-comes in patients with FLT3-mutated relapsed/refractory acute myeloid leukemia: Results from the ADMIRAL study	Time limit
#20	Economic burden of not testing for FLT3 to treat acute myeloid leukemia	Outcome
#21	Overall survival (OS) and quality of life (QOL) of older adults diagnosed with acute myeloid leukemia (AML) and treated under conditions of usual clinical practice: Interim report of the SVLMA study	Population
#22	Oral arsenic trioxide incorporation into frontline treatment with all-trans retinoic acid and chemotherapy in newly diagnosed acute promyelocytic leukemia: A 5-year prospective study	Population
#23	The stromal microenvironment provides an escape route from FLT3 inhibitors through the GAS6-AXL-STAT5 axis	Outcome
#24	Automated decision tree to evaluate genetic abnormalities when determining prognostic risk in acute myeloid leukemia	Outcome
#25	Midostaurin: A New Oral Agent Targeting FMS-Like Tyrosine Kinase 3-Mutant Acute Myeloid Leukemia	Outcome

#26	Phase 1/2 study of pacritinib, a next generation JAK2/FLT3 inhibitor, in myelofibrosis or other myeloid malignancies	Population
#27	Maintenance lenalidomide in combination with 5-azacitidine as post-remission therapy for acute myeloid leukaemia	Population
#28	Internal tandem duplication of the FLT3 gene confers poor overall survival in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline-based chemotherapy: an International Consortium on Acute Promyelocytic Leukemia study	Outcome
#29	Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia	Outcome
#30	Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: A study by the german acute myeloid leukemia cooperative group	Population
#31	PCN485 PATIENT-REPORTED OUTCOMES AND THEIR RELATIONSHIP WITH CLINICAL OUTCOMES IN PATIENTS WITH FLT3-MUTATED (FLT3MUT+) RELAPSED/REFRACTORY (R/R) ACUTE MYELOID LEUKEMIA (AML): RESULTS FROM THE PHASE 3 ADMIRAL STUDY	Time limit
#32	The relationship between hospitalization and patient-reported outcomes (PROs) in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) acute myeloid leukemia (AML): results from the phase 3 admiral study	Time limit
#33	The relationship between transplant status and patient-reported outcomes in patients with FLT3-mutated relapsed/refractory (R/R) acute myeloid leukemia (AML): results from the phase 3 admiral study	Time limit
#34	Quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis of quizartinib vs salvage chemotherapy in patients with relapsed/refractory (R/R) FLT3-ITD acute myeloid leukemia (AML)	Outcome
#35	Cost-Effectiveness Analysis of Gilteritinib Versus Salvage Chemotherapy (SC) for the Treatment of Relapsed or Refractory (R/R) FLT3-Mutated (FLT3mut+) Acute Myeloid Leukemia (AML)	Outcome
#36	A phase Ib/II clinical evaluation of Ponatinib in combination with 5- Azacitidine in patients failing prior therapy for FLT3-ITD+acute myeloid leukaemia (AMLM21)	Outcome
#37	Cost-effectiveness of midostaurin in the treatment of newly diagnosed FLT3-mutated acute myeloid leukemia in the United States	Outcome

Table 93 summarises the three HRQoL studies identified in the global HRQoL SLR (26, 99, 100). One of the studies was of newly diagnosed *FLT3+* AML patients (100), another was of r/r *FLT3+* AML patients (99). One of the studies was of newly diagnosed *FLT3+* AML patients (100), another was of r/r *FLT3+* AML patients (26, 99, 100) and the third study included both newly diagnosed and r/r patients with *FLT3*-ITD+ AML (26). Each of the studies used a variety of elicitation instruments. FACT-Leu and EQ-5D were used in all three studies.

Table 93 Summary of health-related quality of life studies in the global SLR

Study Reference	Study design	Population	Intervention	QoL measures	Subscale	Timepoint	HRQoL value
Horvath Walsh 2019 (26)	Observational study	FLT3-ITD+ AML	Non-interventional	FACT-Leu	Physical well-being	Point-in time survey	12

		sub-group		FACT-Leu	Social well-being	Point-in time survey	18.2
				FACT-Leu	Emotional well-being	Point-in time survey	10.3
				FACT-Leu	Functional well-being	Point-in time survey	13.3
				FACT-G	NA	Point-in time survey	53.8
				FACT-G	Leukaemia-specific	Point-in time survey	31.7
				FACT-G	Trial outcome index	Point-in time survey	70.9
				FACT-G	Overall	Point-in time survey	85.5
				CTSQ	Therapy expectations	Point-in time survey	67.1
				CTSQ	Therapy satisfaction	Point-in time survey	62.2
				CTSQ	Feelings about side effects	Point-in time survey	40.2
				EQ-5D	VAS	Point-in time survey	47.6
				EQ-5D	NR	Point-in time survey	0.64
Ritchie 2023 (99)	Open label, multi-centre, randomised	FLT3+ R/R AML	Gilteritinib	FACT-Leu	Total	Baseline	Mean (SD); median (lower limit, upper limit): 122.1 (26.08); 123 (28,160)
			Salvage chemotherapy	FACT-Leu	Total	Baseline	Mean (SD); median (lower limit, upper limit): 118.5 (25.62); 125.8 (58,173)

Gilteritinib	FACT-Leu	Total	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 123.8 (27.44); 128 (22,173)
Salvage chemo-therapy	FACT-Leu	Total	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 124.2 (22.58); 123 (84,161)
Gilteritinib	FACT-Leu	Total	mEOT	Mean (SD); median (lower limit, upper limit): 116 (30.23); 118 (28,174)
Salvage chemo-therapy	FACT-Leu	Total	mEOT	Mean (SD); median (lower limit, upper limit): 113.8 (25.41); 115 (46,161)
Gilteritinib	FACT-Leu	TOI	Baseline	Mean (SD); median (lower limit, upper limit): 83.6 (20.2); 85 (26,121)
Salvage chemo-therapy	FACT-Leu	TOI	Baseline	Mean (SD); median (lower limit, upper limit): 81.1 (19.86); 83 (17,113)
Gilteritinib	FACT-Leu	TOI	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 85.2 (21.14); 85 (5,122)
Salvage chemo-therapy	FACT-Leu	TOI	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 85.3 (16.08); 84 (47,112)
Gilteritinib	FACT-Leu	TOI	mEOT	Mean (SD); median (lower limit, upper limit): 79 (24.07); 83 (5,124)
Salvage chemo-therapy	FACT-Leu	TOI	mEOT	Mean (SD); median (lower limit, upper limit): 76.5 (19.03); 79 (20,110)

Gilteritinib	FACT-Leu	General	Baseline	Mean (SD); median (lower limit, upper limit): 74.6 (17.28); 76 (29,108)
Salvage chemotherapy	FACT-Leu	General	Baseline	Mean (SD); median (lower limit, upper limit): 72.5 (17.74); 73 (18,107)
Gilteritinib	FACT-Leu	General	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 75.9 (17.69); 78.4 (10,108)
Salvage chemotherapy	FACT-Leu	General	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 74.7 (16.53); 79 (44,102)
Gilteritinib	FACT-Leu	General	mEOT	Mean (SD); median (lower limit, upper limit): 70.7 (18.83); 69.7 (26,106)
Salvage chemotherapy	FACT-Leu	General	mEOT	Mean (SD); median (lower limit, upper limit): 69.5 (17.05); 68 (20,101)
Gilteritinib	FACT-Leu	PWB	Baseline	Mean (SD); median (lower limit, upper limit): 21.4 (5.92); 23 (0,28)
Salvage chemotherapy	FACT-Leu	PWB	Baseline	Mean (SD); median (lower limit, upper limit): 21.3 (6.26); 23 (2,28)
Gilteritinib	FACT-Leu	PWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 22.4 (5.73); 24.5 (1,28)
Salvage chemotherapy	FACT-Leu	PWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 22.7 (3.99); 23 (12,28)
Gilteritinib	FACT-Leu	PWB	mEOT	Mean (SD); median (lower limit, upper limit):

				19.9 (6.83); 22 (0,28)
Salvage chemo-therapy	FACT-Leu	PWB	mEOT	Mean (SD); median (lower limit, upper limit): 20.1 (6.24); 22 (2,28)
Gilteritinib	FACT-Leu	EWB	Baseline	Mean (SD); median (lower limit, upper limit): 16.2 (4.99); 17 (3,24)
Salvage chemo-therapy	FACT-Leu	EWB	Baseline	Mean (SD); median (lower limit, upper limit): 15.9 (4.82); 17 (0,24)
Gilteritinib	FACT-Leu	EWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 17.2 (4.72); 18 (1,24)
Salvage chemo-therapy	FACT-Leu	EWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 17.3 (4.27); 18 (9,24)
Gilteritinib	FACT-Leu	EWB	mEOT	Mean (SD); median (lower limit, upper limit): 16 (5.34); 17 (0,24)
Salvage chemo-therapy	FACT-Leu	EWB	mEOT	Mean (SD); median (lower limit, upper limit): 15.6 (5.72); 17 (0,24)
Gilteritinib	FACT-Leu	FWB	Baseline	Mean (SD); median (lower limit, upper limit): 14.7 (6.82); 14 (1,28)
Salvage chemo-therapy	FACT-Leu	FWB	Baseline	Mean (SD); median (lower limit, upper limit): 13.8 (7.15); 13 (0,28)
Gilteritinib	FACT-Leu	FWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 15 (6.81); 14 (0,28)

Salvage chemo-therapy	FACT-Leu	FWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 13.1 (5.9); 13 (4,25)
Gilteritinib	FACT-Leu	FWB	mEOT	Mean (SD); median (lower limit, upper limit): 16 (13.9); 13 (0,28)
Salvage chemo-therapy	FACT-Leu	FWB	mEOT	Mean (SD); median (lower limit, upper limit): 12.2 (5.97); 11 (3,24)
Gilteritinib	FACT-Leu	SWB	Baseline	Mean (SD); median (lower limit, upper limit): 22.3 (5.8); 24 (0,28)
Salvage chemo-therapy	FACT-Leu	SWB	Baseline	Mean (SD); median (lower limit, upper limit): 21.5 (6.66); 23.3 (0,28)
Gilteritinib	FACT-Leu	SWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 21.4 (6.45); 23.3 (0,28)
Salvage chemo-therapy	FACT-Leu	SWB	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 21.6 (6.04); 21 (5,28)
Gilteritinib	FACT-Leu	SWB	mEOT	Mean (SD); median (lower limit, upper limit): 21 (6.2); 22 (0,28)
Salvage chemo-therapy	FACT-Leu	SWB	mEOT	Mean (SD); median (lower limit, upper limit): 21.6 (5.34); 22 (7,28)
Gilteritinib	FACT-Leu	Leu-S	Baseline	Mean (SD); median (lower limit, upper limit): 47.6 (10.57); 49 (14,65)
Salvage chemo-therapy	FACT-Leu	Leu-S	Baseline	Mean (SD); median (lower limit, upper limit):

				46 (10.19); 47 (10,65)
Gilteritinib	FACT-Leu	Leu-S	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 47.9 (11.72); 50 (1,67)
Salvage chemo-therapy	FACT-Leu	Leu-S	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 49.5 (8.62); 54 (26,59)
Gilteritinib	FACT-Leu	Leu-S	mEOT	Mean (SD); median (lower limit, upper limit): 45.2 (13.37); 48 (1,68)
Salvage chemo-therapy	FACT-Leu	Leu-S	mEOT	Mean (SD); median (lower limit, upper limit): 44.3 (10.26); 46 (12,60)
Gilteritinib	EQ-5D	VAS score	Baseline	Mean (SD); median (lower limit, upper limit): 63.9 (24.56); 70 (1,100)
Salvage chemo-therapy	EQ-5D	VAS score	Baseline	Mean (SD); median (lower limit, upper limit): 62.9 (24.15); 69 (0,100)
Gilteritinib	EQ-5D	VAS score	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 65.5 (22.71); 70 (5,100)
Salvage chemo-therapy	EQ-5D	VAS score	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 67.2 (23.7); 67 (19,98)
Gilteritinib	EQ-5D	VAS score	mEOT	Mean (SD); median (lower limit, upper limit): 62.1 (24.14); 69 (0,100)
Salvage chemo-therapy	EQ-5D	VAS score	mEOT	Mean (SD); median (lower limit, upper limit): 61.9 (22.42); 62.5 (0,98)

Gilteritinib	BFI	Total	Baseline	Mean (SD); median (lower limit, upper limit): 3 (2.56); 2.6 (0,9)
Salvage chemo-therapy	BFI	Total	Baseline	Mean (SD); median (lower limit, upper limit): 2.7 (2.47); 2 (0,10)
Gilteritinib	BFI	Total	Cycle1, Day 8	Mean (SD); median (lower limit, upper limit): 2.5 (2.21); 2.1 (0,10). Mean change from baseline: -0.39
Salvage chemo-therapy	BFI	Total	Cycle1, Day 8	Mean (SD); median (lower limit, upper limit): 3.7 (2.49); 3.6 (0,10). Mean change from baseline:0.89
Gilteritinib	BFI	Total	Cycle1, Day 15	Mean change from baseline: -0.33
Salvage chemo-therapy	BFI	Total	Cycle1, Day 15	Mean change from baseline: 1.05
Gilteritinib	BFI	Total	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 2.9 (2.6); 2.3 (0,10). Mean change from baseline: 0.03
Salvage chemo-therapy	BFI	Total	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 2.5 (2.04); 2.2 (0,6). Mean change from baseline: 0.86
Gilteritinib	BFI	Total	Cycle1, Day 15	Mean change from baseline: 0.28

Salvage chemo-therapy	BFI	Total	Cycle1, Day 15	Mean change from baseline: 1.13
Gilteritinib	BFI	Total	mEOT	Mean (SD); median (lower limit, upper limit): 4 (2.69); 3.8 (0,10). Mean change from baseline: 0.21
Salvage chemo-therapy	BFI	Total	mEOT	Mean (SD); median (lower limit, upper limit): 4 (2.79); 3.4 (0,10). Mean change from baseline: 0.49
Gilteritinib	BFI	Sever-ity	Baseline	Mean (SD); median (lower limit, upper limit): 3.5 (2.64); 3 (0,9)
Salvage chemo-therapy	BFI	Sever-ity	Baseline	Mean (SD); median (lower limit, upper limit): 3.2 (2.67); 3 (0,10)
Gilteritinib	BFI	Sever-ity	Cycle1, Day 8	Mean (SD); median (lower limit, upper limit): 3 (2.41); 2.7 (0,10). Mean change from baseline: -0.34
Salvage chemo-therapy	BFI	Sever-ity	Cycle1, Day 8	Mean (SD); median (lower limit, upper limit): 4.2 (2.6); 4 (0,10). Mean change from baseline: 1.05
Gilteritinib	BFI	Sever-ity	Cycle1, Day 15	Mean change from baseline: -0.28
Salvage chemo-therapy	BFI	Sever-ity	Cycle1, Day 15	Mean change from baseline: 1.08
Gilteritinib	BFI	Sever-ity	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit):

				3.3 (2.71); 3 (0,10). Mean change from baseline: 0
Salvage chemo-therapy	BFI	Sever-ity	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 3.1 (2.65); 2.3 (0,8). Mean change from baseline: 0.73
Gilteritinib	BFI	Sever-ity	Cycle1, Day 15	Mean change from baseline: 0.31
Salvage chemo-therapy	BFI	Sever-ity	Cycle1, Day 15	Mean change from baseline: 0.83
Gilteritinib	BFI	Sever-ity	mEOT	Mean (SD); median (lower limit, upper limit): 4.4 (2.73); 4.3 (0,10). Mean change from baseline: 0.17
Salvage chemo-therapy	BFI	Sever-ity	mEOT	Mean (SD); median (lower limit, upper limit): 4.4 (2.92); 4.7 (0,10). Mean change from baseline: 0.49
Gilteritinib	BFI	Inter-fer-ence	Baseline	Mean (SD); median (lower limit, upper limit): 2.8 (2.66); 2.2 (0,10)
Salvage chemo-therapy	BFI	Inter-fer-ence	Baseline	Mean (SD); median (lower limit, upper limit): 2.5 (2.5); 1.7 (0,9)
Gilteritinib	BFI	Inter-fer-ence	Cycle1, Day 8	Mean (SD); median (lower limit, upper limit): 2.3 (2.31); 1.5 (0,10). Mean change from baseline: -0.32

Salvage chemo-therapy	BFI	Inter-fer-ence	Cycle1, Day 8	Mean (SD); median (lower limit, upper limit): 3.4 (2.58); 3.3 (0,10). Mean change from baseline: 0.85
Gilteritinib	BFI	Inter-fer-ence	Cycle1, Day 15	Mean change from baseline: -0.31
Salvage chemo-therapy	BFI	Inter-fer-ence	Cycle1, Day 15	Mean change from baseline: 1.08
Gilteritinib	BFI	Inter-fer-ence	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 2.7 (2.69); 1.8 (0,10). Mean change from baseline: 0.06
Salvage chemo-therapy	BFI	Inter-fer-ence	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 2.2 (1.97); 1.5 (0,5). Mean change from baseline: 0.93
Gilteritinib	BFI	Inter-fer-ence	Cycle1, Day 15	Mean change from baseline: 0.29
Salvage chemo-therapy	BFI	Inter-fer-ence	Cycle1, Day 15	Mean change from baseline: 1.25
Gilteritinib	BFI	Inter-fer-ence	mEOT	Mean (SD); median (lower limit, upper limit): 3.8 (2.84); 3.6 (0,10). Mean change from baseline: 0.25
Salvage chemo-therapy	BFI	Inter-fer-ence	mEOT	Mean (SD); median (lower limit, upper limit): 3.8 (2.86); 3.3 (0,10). Mean change from

				baseline: 0.54
Gilteritinib	FACIT-Dys	Dyspnea	Baseline	Mean (SD); median (lower limit, upper limit): 7.4 (8.37); 5 (0,30)
Salvage chemotherapy	FACIT-Dys	Dyspnea	Baseline	Mean (SD); median (lower limit, upper limit): 7.1 (8.46); 4 (0,30)
Gilteritinib	FACIT-Dys	Dyspnea	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 6.1 (6.66); 4 (0,27)
Salvage chemotherapy	FACIT-Dys	Dyspnea	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 7.6 (8.49); 4.5 (0,21)
Gilteritinib	FACIT-Dys	Dyspnea	mEOT	Mean (SD); median (lower limit, upper limit): 9 (8.3); 6 (0,30)
Salvage chemotherapy	FACIT-Dys	Dyspnea	mEOT	Mean (SD); median (lower limit, upper limit): 9.5 (9.72); 6.5 (0,29)
Gilteritinib	FACIT-Dys	Functional limitation	Baseline	Mean (SD); median (lower limit, upper limit): 6.5 (7.99); 3.2 (0,30)
Salvage chemotherapy	FACIT-Dys	Functional limitation	Baseline	Mean (SD); median (lower limit, upper limit): 5.9 (7.89); 3 (0,30)
Gilteritinib	FACIT-Dys	Functional limitation	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 4.9 (6.19); 3 (0,29)
Salvage chemotherapy	FACIT-Dys	Functional limitation	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 5.5 (6.24); 4.5 (0,17)
Gilteritinib	FACIT-Dys	Functional	mEOT	Mean (SD); median

		limita-tion		(lower limit, upper limit): 7.6 (7.82); 5 (0,30)
Salvage chemo-therapy	FACIT-Dys	Func-tional limita-tion	mEOT	Mean (SD); median (lower limit, upper limit): 7.8 (8.8); 4 (0,29)
Gilteritinib	Leukaemia specific symptoms	Dizzi-ness	Baseline	Mean (SD); median (lower limit, upper limit): 0.4 (0.76); 0 (0,4)
Salvage chemo-therapy	Leukaemia specific symptoms	Dizzi-ness	Baseline	Mean (SD); median (lower limit, upper limit): 0.5 (0.95); 0 (0,4)
Gilteritinib	Leukaemia specific symptoms	Dizzi-ness	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 0.6 (0.94); 0 (0,4)
Salvage chemo-therapy	Leukaemia specific symptoms	Dizzi-ness	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 0.4 (0.91); 0 (0,3)
Gilteritinib	Leukaemia specific symptoms	Dizzi-ness	mEOT	Mean (SD); median (lower limit, upper limit): 0.8 (1.11); 0 (0,4)
Salvage chemo-therapy	Leukaemia specific symptoms	Dizzi-ness	mEOT	Mean (SD); median (lower limit, upper limit): 0.6 (0.83); 0 (0,3)
Gilteritinib	Leukaemia specific symptoms	Mouth sores	Baseline	Mean (SD); median (lower limit, upper limit): 0.3 (0.65); 0 (0,4)
Salvage chemo-therapy	Leukaemia specific symptoms	Mouth sores	Baseline	Mean (SD); median (lower limit, upper limit): 0.3 (0.77); 0 (0,4)
Gilteritinib	Leukaemia specific symptoms	Mouth sores	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 0.4 (0.82); 0 (0,4)

Salvage chemo-therapy	Leukaemia specific symptoms	Mouth sores	Cycle 2, day 1	Mean (SD); median (lower limit, upper limit): 0.1 (0.26); 0 (0,1)
Gilteritinib	Leukaemia specific symptoms	Mouth sores	mEOT	Mean (SD); median (lower limit, upper limit): 0.5 (0.95); 0 (0,4)
Salvage chemo-therapy	Leukaemia specific symptoms	Mouth sores	mEOT	Mean (SD); median (lower limit, upper limit): 0.5 (0.92); 0 (0,4)
Gilteritinib	BFI	Total	NR	Mean (95% CI): 0.584 (0.184, 0.984)
Gilteritinib	BFI	Sever-ity	NR	Mean (95% CI): 0.473 (0.074, 0.873)
Gilteritinib	BFI	Inter-fer-ence	NR	Mean (95% CI): 0.644 (0.225, 1.063)
Gilteritinib	BFI	Total	NR	Mean (95% CI): 1.532 (0.274, 2.789)
Gilteritinib	BFI	Sever-ity	NR	Mean (95% CI): 0.947 (-0.368, 2.261)
Gilteritinib	BFI	Inter-fer-ence	NR	Mean (95% CI): 1.822 (0.548, 3.096)
Gilteritinib	FACIT-Dys SF	Dysp-noea	NR	Mean (95% CI): 3.034 (1.533, 4.536)
Gilteritinib	FACIT-Dys SF	Func-tional limita-tion	NR	Mean (95% CI): 2.766 (1.258, 4.275)
Gilteritinib	FACIT-Dys SF	Dysp-noea	NR	Mean (95% CI): 2.904 (-3.048, 8.856)
Gilteritinib	FACIT-Dys SF	Func-tional limita-tion	NR	Mean (95% CI): 3.118 (-2.572, 8.807)
Gilteritinib	FACT-Leu	Total	NR	Mean (95% CI): -6.255 (-10.384, -2.126)

Gilteritinib	FACT-Leu	TOI	NR	Mean (95% CI): -7.08 (-10.391, -3.769)
Gilteritinib	FACT-Leu	Gen-eral	NR	Mean (95% CI): -2.28 (-4.859, 0.299)
Gilteritinib	FACT-Leu	PWB	NR	Mean (95% CI): -2.291 (-3.25, -1.331)
Gilteritinib	FACT-Leu	EWB	NR	Mean (95% CI): -0.105 (-0.825, 0.616)
Gilteritinib	FACT-Leu	FWB	NR	Mean (95% CI): -0.822 (-1.79, 0.147)
Gilteritinib	FACT-Leu	SWB	NR	Mean (95% CI): -0.987 (-0.205, -1.769)
Gilteritinib	FACT-Leu	Leu-S	NR	Mean (95% CI): -3.997 (-5.812, -2.183)
Gilteritinib	FACT-Leu	Total	NR	Mean (95% CI): -14.248 (-25.856, -2.639)
Gilteritinib	FACT-Leu	TOI	NR	Mean (95% CI): -12.01 (-20.996, -3.032)
Gilteritinib	FACT-Leu	Gen-eral	NR	Mean (95% CI): -7.809 (-15.336, -0.282)
Gilteritinib	FACT-Leu	PWB	NR	Mean (95% CI): -3.781 (-6.17, -1.393)
Gilteritinib	FACT-Leu	EWB	NR	Mean (95% CI): -1.361 (-3.113, 0.392)
Gilteritinib	FACT-Leu	FWB	NR	Mean (95% CI): -1.865 (-4.609, 0.879)
Gilteritinib	FACT-Leu	SWB	NR	Mean (95% CI): -0.776 (-3.205, 1.654)
Gilteritinib	FACT-Leu	Leu-S	NR	Mean (95% CI): -6.146 (-11.378, -1.454)
Gilteritinib	EQ-5D	VAS	NR	Mean (95% CI): 5.936 (9.581, 2.29)
Gilteritinib	EQ-5D	VAS	NR	Mean (95% CI): -4.85 (-13.399, 3.699)

Wang 2021 (100)Wang 2021 (100)	Phase 3 trial	ND FLT3+ AML ineligible for Intensive Induction Chemotherapy	Gilteritinib + azacitidine	BFI	NR	Cycle 1, Day 8	Between group difference in favour of gilteritinib + azacitidine:-10 (95% CI -1.9, -0.2); P=.019)
			Azacitidine	BFI	NR	Cycle 1, Day 8	
			Gilteritinib + azacitidine	FACIT-Dys-SF	dyspnoea subscale	Cycle 3, Day 1	Between group difference in favour of azacitidine:-7.7 (95% CI 0.5, 14.8); P=.037
			Azacitidine	FACIT-Dys-SF	dyspnoea subscale	Cycle 3, Day 1	
			Gilteritinib + azacitidine	FACT-Leu Trial Outcome Index	NR	Cycle 2, Day 1	Between group difference in favour of gilteritinib + azacitidine: 8.1 (95% CI 0.5, 15.7); P=.038
			Azacitidine	FACT-Leu Trial Outcome Index	NR	Cycle 2, Day 1	
			Gilteritinib + azacitidine	EQ-5D-5L utility index	NR	Cycle 2, Day 1	Between group difference in favour of gilteritinib + azacitidine: 0.1 (95% CI 0.0, 0.2); P=.049
			Azacitidine	EQ-5D-5L utility index	NR	Cycle 2, Day 1	
			Gilteritinib + azacitidine	Dizziness	NR	Baseline	0.49
			Azacitidine	Dizziness	NR	Baseline	0.63
			Gilteritinib + azacitidine	Mouth sores	NR	Baseline	0.47
			Azacitidine	Mouth sores	NR	Baseline	0.48

Table 94 summarises the utility/disutility data from the seven economic evaluations included in the global SLR which contained HRQoL data (31, 68, 98, 101-104). Five were all in the newly diagnosed FLT3+ population (31, 98, 101-103) and the remaining two of these studies were in the r/r *FLT3+* AML population (31, 98, 101-103). None of the studies were specific to the FLT3-ITD+ population. Four out of seven economic evaluation studies used the same model structure but from different perspectives (31, 98, 101, 102). As a result, there was a significant overlap in terms of the sources of the utility data used in these studies.

Table 94 Utility values reported in economic evaluation studies (global SLR)

Study Reference	Population	Intervention	Utility/Disutility value	Data Source

Tremblay 2018 (98)	Adults with ND FLT3+ AML	Midostaurin+ SOC	**Health state utilities** **Induction treatment** Utility values used in base case (literature): 0.648 Values used in scenario analysis (TTO): 0.162 **Consolidation treatment** Utility values used in base case (literature): 0.710 Values used in scenario analysis (TTO): 0.568 **Monotherapy treatment** Utility values used in base case (literature): 0.810 Values used in scenario analysis (TTO): 0.889 **Complete remission** Utility values used in base case (literature): 0.830 Values used in scenario analysis (TTO): 0.887 **Relapse** Utility values used in base case (literature): 0.530 Values used in scenario analysis (TTO): 0.505 **SCT treatment** Utility values used in base case (literature): 0.613 Values used in scenario analysis (TTO): − 0.210 **SCT recovery** Utility values used in base case (literature): 0.810 Values used in scenario analysis (TTO): 0.748 **Post-SCT recovery** Utility values used in base case (literature): 0.826 Values used in scenario analysis (TTO): 0.715	Uyl-de Groot 1998 (105), Batty 2014, (106) Leunis 2014 (107), Grulke, 2012(55), Pan 2010(108), Crott 2010(56)
NICE TA523 (31)	Adult patients with ND FLT3+ AML	Midostaurin+ Chemotherapy	**Utility values used in the model** Induction treatment: 0.648 Consolidation treatment: 0.710 Monotherapy treatment: 0.810 Complete remission post-1L (No relapse): 0.830 Relapse 0.530 SCT Treatment: 0.613 SCT Recovery: 0.810 Post-SCT Recovery: 0.826	Uyl-de Groot 1998 (105), Batty 2014 (106), Leunis 2014 (107), Grulke, 2012(55), Pan 2010(108), Crott 2010 (56)
NICE TA642 (68)	Adult patients with FLT3+ R/R AML	Gilteritinib	**Health state utilities (sensitivity analysis)** EFS without HSCT: 0.89 Post-event without HSCT:0.51 EFS with HSCT: 0.94	Joshi 2019(109), Janssen 2014(110), Swinburn 2010(111), Doyle 2008(112), Lloyd 2006(113), Nafees 2008(114)

			Post-event with HSCT: 0.51 AML long-term survivors: 0.94 **Age-related utilities** Age 55-64: 0.799 Age 65-74:0.779 Age 75+: 0.726 **Subsequent HSCT disutility** One-time HSCT disutility for patients with subsequent HSCT -0.21 **AE disutilities** Anaemia: -0.119 Dyspnoea: -0.05 Elevated alanine aminotransferase: 0.000 Elevated aspartate aminotransferase: 0.000 Elevated blood phosphocreatine kinase: 0.000 Fatigue: -0.115 Febrile neutropenia: -0.150 Hyperglycaemia: 0.000 Hypertension: -0.153 Hypokalaemia: 0.000 Hyponatraemia: 0.000 Hypophosphatemia: 0.000 Hypotension: -0.153 Leukopenia: -0.090 Neutropenia: -0.090 Neutrophil count decreased: 0.000 Platelet count decreased: 0.000 Pneumonia: -0.153 Sepsis: -0.090 Thrombocytopenia: -0.090 White blood cell count decreased: 0.000	Health state utilities (base-case) were from ADMIRAL(57) but were redacted. Health state utilities (base-case) were from ADMIRAL(57) but were redacted.
Arenaza 2019 (101)	Untreated adult AML patients with mutated FLT3	Midostaurin +SOC (composed of cytarabine (days 1–7) and daunorubicin (days 1–3))	**Utilities associated with treatment phases** Induction: 0.648 Consolidation: 0.710 Maintenance: 0.810 CR post 1st line (no relapse): 0.830 Relapse: 0.780 HSCT: 0.613 HSCT recovery: 0.810 HSCT follow up (after 1st line): 0.826	Uyl-de Groot 1998 (105), Batty 2014 (106), Leunis 2014 (107), NICE 2018 (115), Crott 2010(56), Grulke, 2012(55)
Tremblay 2020(102)	Adult patients with ND FLT3-AML who were candidates for SC	Induction (cytarabine + daunorubicin + midostaurin)+Consolidation (high dose cytarabine	**Health state utilities** **Induction treatment** Baseline (before treatment disutility applied): 0.648 Midostaurin (including disutility): 0.138 SOC (including disutility): 0.124 **Consolidation treatment**	Uyl-de Groot 1998 (105), Batty 2014 (106), Leunis 2014 (107), Grulke, 2012(55), Pan 2010(108), Crott 2010(56)

+ midostaurin)+Maintenance (midostaurin)	Baseline (before treatment disutility applied): 0.710 Midostaurin (including disutility): 0.149 SOC (including disutility): 0.120 **Maintenance monotherapy treatment** Baseline (before treatment disutility applied): 0.810 Midostaurin (including disutility): 0.798 SOC (including disutility): 0.797 **Complete remission** Baseline (before treatment disutility applied): 0.830 Midostaurin (including disutility): 0.830 SOC (including disutility): 0.830 **Relapse** Baseline (before treatment disutility applied): 0.530 Midostaurin (including disutility): 0.530 SOC (including disutility): 0.530 **HSCT Treatment** Baseline (before treatment disutility applied): 0.613 Midostaurin (including disutility): 0.613 SOC (including disutility): 0.613 **HSCT Recovery** Baseline (before treatment disutility applied): 0.743 Midostaurin (including disutility): 0.743 SOC (including disutility): 0.743 **Post-HSCT Recovery** Baseline (before treatment disutility applied)0.759 Midostaurin (including disutility): 0.759 SOC (including disutility): 0.759 **HSCT Relapse** Baseline (before treatment disutility applied): 0.530 Midostaurin (including disutility): 0.530 SOC (including disutility): 0.530 **Adverse event related disutility** Platelet count decreased: -0.11 Neutrophil count: -0.16 Haemoglobin: -0.16 Febrile neutropenia: -0.20 Leukopenia NOS: -0.16 Lymphopenia: -0.16 Diarrhoea NOS: -0.20 Hypokalaemia: -0.17 Alanine aminotransferase increased: 0.00

			Dermatitis exfoliative NOS: -0.17 Fatigue: -0.17 Hyperglycaemia NOS: -0.17 Pneumonitis NOS: -0.20 Nausea: -0.17 Hyponatremia: -0.17 Blood bilirubin increased: -0.17 Infection: -0.20 Hypophosphatasaemia: -0.17 Gamma-glutamyl transferase increased: -0.17 Hypocalcaemia: -0.17 Radiation mucositis: -0.17 Hypoalbuminemia: -0.17 Syncope: -0.17 QT prolongation: -0.17	
Stein 2019 (103)	Adult patients (≥18 years of age) with ND FLT3+ AML and eligible for SC with cytarabine + daunorubicin	Midostaurin + cytarabine + daunorubicin	**Health state utility inputs:** Active disease: 0.26 CR: 0.87 Relapse and post-relapse: 0.62 **SCT utility inputs:** SCT procedure (applied for 1 month): 0.16 Post-SCT (applied for 6 months): 0.40 **Adverse event disutility inputs** Midostaurin treatment arm: 0.29 Placebo treatment arm: 0.29	Stein 2018 (116), Stone 2017(2)
Pandya 2021(104)	Adult patients with R/R FLT3mut+ AML	Gilteritinib	**Utility inputs for health states:** EFS without HSCT: 0.84 Post event without HSCT: 0.77 EFS with HSCT: 0.86 Post event with HSCT: 0.80 Long-term survivors: 0.86 **Age-related utilities:** Age 55-64 years: 0.83 Age 65-74 years: 0.82 Age ≥75 years: 0.76 **Disutility associated with AEs:** Gilteritinib: −0.21 SC: −0.14 43 BSC: 0.00 **Disutility from HSCT:** –0.21 for 6 months	Perl 2019(57), Janssen 2014(110), Swinburn 2020(111), Doyle 2008(112), Lloyd 2006(113), Joshi 2019(109).

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

An SLR was conducted to support this HTA submission for quizartinib in newly diagnosed AML FLT3-ITD+ patients. The objective of this SLR was to identify relevant economic evidence for patients with *FLT3*+ AML to guide the development of an economic model consistent with current practices.

J.1.1 Systematic search for cost effectiveness and cost and health care resource

J.1.1.1 Objective

The economic SLR answers the following research questions:

- Cost-effectiveness studies search:
    - What are the modelling techniques (e.g. structure, input parameters and model outputs) used in economic evaluations of currently available treatments for adults with AML that is FLT3+?
- Cost and healthcare resource search:
    - What is the direct and indirect cost associated with the management of adult patients with AML that is FLT3+?
    - What is the healthcare resource utilisation associated with the management of adult patients with AML that is FLT3+ in terms of at least:
        - Hospitalisation (inpatient, outpatient, emergency room [ER])
        - General practitioners (GPs), specialists, nurse visits
        - Diagnostic test
        - Procedures (e.g., stem cell transplant)
        - Management of treatment toxicity and complications

J.1.1.2 Methods

The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (76), the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance (77) for undertaking reviews in health care, the PRISMA guidelines (78) and the methods for systematic reviews as specified by the NICE (79). The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (76), the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance (77) for undertaking reviews in health care, the PRISMA guidelines (78) and the methods for systematic reviews as specified by the NICE (79).

J.1.1.3 Information sources

J.1.1.3.1 Bibliographic databases

The OVID SP® platform was used to conduct the literature searches. The OVID SP® platform is a search platform that provides standardised access to a wide range of literature databases and is an accepted tool for use in a SLR. The databases in Table 95 were used to conduct the SLR searches, which are in line with recommendations from the Cochrane Collaboration (Higgins et al., 2019) and the NICE (National Institute for Health and Care Excellence (NICE), 2022) guidance.

Table 95 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
MEDLINE	OVID	1946 until today	09.05.2023
Embase	OVID	1974 until today	09.05.2023
CENTRAL	OVID	April 2023	09.05.2023
CDSR	OVID	2005 to May 2, 2023	09.05.2023
DARE	OVID	– until 1st Quarter, 2016	09.05.2023
NHS EED	OVID	– until 1st Quarter, 2016	09.05.2023
HTA	OVID	2011 to 4th Quarter, 2016	09.05.2023
EconLit	OVID	1886 until today	09.05.2023

Notes: The Database of Abstracts of Reviews of Effects, the Health Technology Assessment Data-base and the NHS EED are no longer updated since 2016.

J.1.1.3.2 Trial registries

The search of trial registries is detailed in Appendix H.1.3.2. A list of included trial registries is provided in Table 84.

J.1.1.3.3 HTA database

The search of HTA databases is detailed in Appendix I.1.1.3.3. A list of included trial registries is provided in Table 85.

J.1.1.3.4 Conference proceedings

The search of conference proceedings is detailed in Appendix H.1.3.4, H.1.3.2. A list of included conference material is provided in Table 86.

J.1.1.3.5 Other

A hand-search of the reference lists of relevant studies, key SLRs, meta-analyses and network meta-analyses publications was also conducted.

Table 96 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	AML, Midostaurin	09.05.2023

J.1.2 Search strategies

As recommended by various HTA agencies such as NICE (79), SMC (80), G-BA (81) and for comprehensiveness of the data collection, search strategies were developed through the combination of free text words, indexing terms (e.g. medical subject headings [MeSH] terms for Medline and Emtree terms for Embase] and by using Boolean terms (e.g. 'and', 'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the inclusion/exclusion criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax and presented in As recommended by various HTA agencies such as NICE (79), SMC (80), G-BA (81) and for comprehensiveness of the data collection, search strategies were developed through the combination of free text words, indexing terms (e.g. medical subject headings [MeSH] terms for Medline and Emtree terms for Embase] and by using Boolean terms (e.g. 'and', 'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the inclusion/exclusion criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax and presented in Table 75-Table 79. The searches were run in OVID.

The systematic literature searches were performed using a pre-defined search strategy to identify eligible studies. The clinical SLR searches were not limited by date or geographical location. The eligibility criteria are specified in Table 80.

Table 97. Economic SLR – Embase

#	Query	Results
1	exp acute myeloid leukemia/	66,157
2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kf.	148,865
3	acute.ti,ab,kf.	2,024,290
4	2 and 3	103,851
5	(AML or ANLL).ti,ab,kf.	85,001
6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,585
7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	809
8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or diguglielmo$ or erythremic myelos$).ti,ab,kf.	5,950
9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	155
10	exp granulocytic sarcoma/	3,283

11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	6,618
12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	52
13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	2,249
14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	1,351
15	exp secondary acute myeloid leukemia/	1,746
16	(sAML or AML-MRC or tAML).ti,ab,kf.	1,705
17	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	161,547
18	CD135 antigen/	10,807
19	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	17,171
20	18 or 19	19,526
21	exp economic aspect/	2,428,773
22	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,ab,kw.	1,551,770
23	exp "cost"/	399,266
24	cost$.ti,kw.	219,010
25	"cost of illness"/	21,158
26	cost of illness.ab,ti,kw.	4,665
27	exp budget/	33,629
28	budget*.ti,ab,kw.	47,051
29	statistical model/	173,324
30	exp economic model/	3,707
31	(economic adj2 model$).ab,ti,kw.	8,272
32	Monte Carlo method/	50,553
33	monte carlo.ti,ab,kw.	61,463
34	markov$.ti,ab,kw.	40,789
35	decision theory/	1,847
36	decision tree/	21,266
37	(decision adj2 (tree$ or analys$ or model$)).ti,ab.	46,390
38	(cba or cea or cua or cma or cca).ti,ab.	79,618
39	(value adj2 (money or monetary)).ti,ab,kw.	4,064
40	(partition$ survival or PSM or PartSA).ti,ab.	12,369
41	exp patient simulation/	1,728
42	Microsimulation.ti,ab,kw.	2,688
43	patient level simulation.ti,ab,kw.	244
44	discrete event simulation.ti,ab,kw.	1,446

45	"cost minimization analysis"/	3,978
46	"cost effectiveness analysis"/	179,841
47	"cost benefit analysis"/	93,821
48	(cost$ adj2 (effective$ or utilit$ or analys$ or benefit$ or minimi$ or unit$ or estimat$ or variable$)).ab,kw.	295,806
49	(quality adjusted or adjusted life year$ or QALY$).ti,ab,kw.	40,115
50	quality adjusted life year/	35,103
51	(ICER$ or incremental cost-effectiveness ratio$).ti,ab,kw.	21,425
52	(qaly$ or qald$ or qale$ or qtime$ or life year or life years).ti,ab,kw.	44,367
53	quality adjusted life.ti,ab,kw.	26,418
54	disability-adjusted life year/	4,343
55	disability adjusted life.ti,ab,kw.	6,289
56	daly$1.ti,ab,kw.	6,050
57	(utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or score$ or weight)).ti,ab,kw.	25,378
58	disutili$.ti,ab,kw.	1,233
59	(net monetar$ benefit$ or INMB).ti,ab,kw.	1,091
60	exp terminal care/	84,474
61	((hospice$ or terminal or pallative) adj2 care).ti,ab,kw.	11,272
62	exp "Health care cost"/	336,090
63	Hospitalization cost/	9,864
64	Nursing cost/	207
65	Health care utilization/	93,000
66	"Drug cost"/	85,367
67	exp Resource allocation/	24,736
68	Resource management/	11,747
69	((healthcare or health care or resourc$ or service$ or hospital$) adj2 (utili$ or us$)).ti,ab,kw.	273,483
70	"Length of stay"/	264,624
71	((length or duration or extended or prolonged) adj stay).ti,ab,kw.	2,197
72	or/21-71	4,088,138
73	17 and 20 and 72	1,021
74	exp animal/	30,593,845
75	exp human/	25,421,121
76	74 not (74 and 75)	5,172,724
77	case report/	2,895,892
78	editorial/	742,861
79	(editorial or note).pt.	1,711,679
80	77 or 78 or 79	4,566,607

81	73 not 76	1,012
82	81 not 80	936
83	limit 82 to conference abstract	690
84	limit 83 to yr="2020 -Current"	332
85	82 not 83	246
86	84 or 85	578
87	limit 86 to yr="2012 -Current"	539

Table 98. Economic SLR – MEDLINE

#	Searches	Results
1	exp leukemia, myeloid, acute/	63,871
2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kf.	99,379
3	acute.ti,ab,kf.	1,425,762
4	2 and 3	64,643
5	(AML or ANLL).ti,ab,kf.	41,601
6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kf.	1,670
7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kf.	517
8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or diguglielmo$ or erythremic myelos$).ti,ab,kf.	5,563
9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kf.	98
10	exp Sarcoma, Myeloid/	1,331
11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kf.	3,399
12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kf.	38
13	(chloroma$ or granulocytic sarcoma$).ti,ab,kf.	1,895
14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kf.	794
15	(sAML or AML-MRC or tAML).ti,ab,kf.	544
16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	105,017
17	exp fms-Like Tyrosine Kinase 3/	3,406
18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	7,573
19	17 or 18	7,931
20	exp Economics, Medical/	14,389
21	exp economics, hospital/	25,709
22	economics, nursing/	4,013

23	economics, pharmaceutical/	3,102
24	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,ab,kw.	1,196,259
25	exp "Costs and Cost Analysis"/	264,225
26	cost$.ti,kw.	155,041
27	exp budgets/	14,108
28	budget*.ti,ab,kw.	35,305
29	"fees and charges"/	9,230
30	exp Models, Economic/	16,201
31	(economic adj2 model$).ab,ti,kw.	5,476
32	Monte Carlo method/	32,106
33	monte carlo.ti,ab,kw.	58,275
34	markov chains/	15,944
35	markov$.ti,ab,kw.	31,775
36	exp decision theory/	13,204
37	(decision adj2 (tree$ or analys$ or model$)).ti,ab.	33,512
38	(cba or cea or cua or cma or cca).ti,ab.	54,341
39	(value adj2 (money or monetary)).ti,ab,kw.	2,990
40	(partition$ survival or PSM or PartSA).ti,ab.	7,960
41	exp patient simulation/	5,487
42	Microsimulation.ti,ab,kw.	1,765
43	patient level simulation.ti,ab,kw.	102
44	discrete event simulation.ti,ab,kw.	918
45	(cost$ adj2 (effective$ or utilit$ or analys$ or benefit$ or minimi$ or unit$ or estimat$ or variable$)).ti,ab,kw.	224,337
46	Value of life/	5,804
47	(ICER$ or incremental cost-effectiveness ratio$).ti,ab,kw.	12,168
48	quality adjusted life years/	15,594
49	(quality adjusted or qaly$ or qald$ or qale$ or qtime$ or life year or life years).ti,ab,kw.	28,215
50	disability-adjusted life years/	175
51	disability adjusted life.ti,ab,kw.	5,096
52	daly$1.ti,ab,kw.	4,530
53	(utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or score$ or weight)).ti,ab,kw.	15,665

54	disutili$.ti,ab,kw.	611
55	(net monetar$ benefit$ or INMB).ti,ab,kw.	663
56	exp terminal care/	56,794
57	((hospice$ or terminal or pallative) adj2 care).ti,ab,kw.	6,971
58	Resource allocation/	9,378
59	Health Resources/	14,676
60	((healthcare or health care or resourc$ or service$ or hospital$) adj2 (utili$ or us$)).ti,ab,kw.	172,955
61	"Length of stay"/	102,081
62	((length or duration or extended or prolonged) adj stay).ti,ab,kw.	1,240
63	or/20-62	1,798,878
64	16 and 19 and 63	73
65	animals/ not humans/	5,085,699
66	Editorial/ or Historical Article/ or case reports/	3,335,008
67	(case reports or historical article or editorial).pt.	3,335,008
68	66 or 67	3,335,008
69	64 not 65	72
70	69 not 68	69
71	limit 70 to yr="2012 -Current"	63

Table 99. Economic SLR – CENTRAL, CDSR, HTA and NHS EED

#	Query	Results from 9 May 2023
1	exp leukemia, myeloid, acute/	1,956
2	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kw.	6,903
3	acute.ti,ab,kw.	160,766
4	2 and 3	5,355
5	(AML or ANLL).ti,ab,kw.	4,880
6	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kw.	274
7	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kw.	9
8	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or diguglielmo$ or erythremic myelos$).ti,ab,kw.	13
9	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kw.	0
10	exp Sarcoma, Myeloid/	1

11	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kw.	110
12	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kw.	1
13	(chloroma$ or granulocytic sarcoma$).ti,ab,kw.	24
14	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kw.	8
15	(sAML or AML-MRC or tAML).ti,ab,kw.	117
16	1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	7,221
17	exp fms-Like Tyrosine Kinase 3/	71
18	(cd135 or flt3 or flt 3 or fms like tyrosine kinase 3).ti,ab,kf.	719
19	17 or 18	723
20	exp Economics, Medical/	114
21	exp economics, hospital/	1,941
22	economics, nursing/	21
23	economics, pharmaceutical/	292
24	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,ab,kw.	122,736
25	exp "Costs and Cost Analysis"/	30,608
26	cost$.ti,kw.	39,315
27	exp budgets/	100
28	budget*.ti,ab,kw.	1,495
29	"fees and charges"/	79
30	exp Models, Economic/	2,266
31	(economic adj2 model$).ab,ti,kw.	668
32	Monte Carlo method/	754
33	monte carlo.ti,ab,kw.	979
34	markov chains/	2,408
35	markov$.ti,ab,kw.	1,881
36	exp decision theory/	1,045
37	(decision adj2 (tree$ or analys$ or model$)).ti,ab.	2,579
38	(cba or cea or cua or cma or cca).ti,ab.	3,173
39	(value adj2 (money or monetary)).ti,ab,kw.	366
40	(partition$ survival or PSM or PartSA).ti,ab.	647
41	exp patient simulation/	576
42	Microsimulation.ti,ab,kw.	159
43	patient level simulation.ti,ab,kw.	24
44	discrete event simulation.ti,ab,kw.	78

45	(cost$ adj2 (effective$ or utilit$ or analys$ or benefit$ or minimi$ or unit$ or estimat$ or variable$)).ti,ab,kw.	48,722
46	Value of life/	161
47	(ICER$ or incremental cost-effectiveness ratio$).ti,ab,kw.	3,693
48	quality adjusted life years/	5,188
49	(quality adjusted or qaly$ or qald$ or qale$ or qtime$ or life year or life years).ti,ab,kw.	7,498
50	disability-adjusted life years/	3
51	disability adjusted life.ti,ab,kw.	295
52	daly$1.ti,ab,kw.	232
53	(net monetar$ benefit$ or INMB).ti,ab,kw.	228
54	exp terminal care/	729
55	((hospice$ or terminal or pallative) adj2 care).ti,ab,kw.	792
56	Resource allocation/	106
57	Health Resources/	723
58	((healthcare or health care or resourc$ or service$ or hospital$) adj2 (utili$ or us$)).ti,ab,kw.	22,742
59	"Length of stay"/	11,220
60	((length or duration or extended or prolonged) adj stay).ti,ab,kw.	124
61	or/20-60	156,484
62	16 and 19 and 61	31
63	animals/ not humans/	2,690
64	Editorial/ or Historical Article/ or case reports/	112
65	(case reports or historical article or editorial).pt.	3,370
66	64 or 65	3,378
67	62 not 63	31
68	67 not 66	31
69	limit 68 to yr="2012 -Current"	28
70	remove duplicates from 68	31

Table 100. Economic SLR – Econlit

#	Query	Results from 9 May 2023
1	((leukemia$ or leukaemia$) adj3 (myeloid or myelogenous or nonlymphocytic or non-lymphocytic or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or monoblastic or monocytic or erythroid or erythroblastic or eosinophilic or basophilic or myelomonocytic or megakaryoblastic or megakaryocytic)).ti,ab,kw.	12
2	acute.ti,ab,kw.	1,943
3	1 and 2	8
4	(AML or ANLL).ti,ab,kw.	97

5	((leukemia$ or leukaemia$) adj3 (schilling or granulocytic)).ti,ab,kw.	0
6	((leukemia$ or leukaemia$) adj3 mast cell$).ti,ab,kw.	0
7	(erythroleukemia$ or erythroleukaemia$ or di guglielmo$ or diguglielmo$ or erythremic myelos$).ti,ab,kw.	2
8	((leukemia$ or leukaemia$) adj3 pure erythroid).ti,ab,kw.	0
9	(myeloid adj3 (sarcoma$ or cell tumor$ or cell tumour$ or neoplasm$)).ti,ab,kw.	0
10	((acute panmyelosis and myelofibrosis) or APMF).ti,ab,kw.	0
11	(chloroma$ or granulocytic sarcoma$).ti,ab,kw.	0
12	(blastic plasmacytoid dendritic cell$ or BPDCN or natural killer cell leukemia$ or natural killer cell leukaemia$ or natural killer lymphoma$).ti,ab,kw.	0
13	(sAML or AML-MRC or tAML).ti,ab,kw.	0
14	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	105
15	limit 14 to yr="2012 -Current"	82

J.1.3 Systematic selection of studies

J.1.3.1 Eligibility criteria

Selection of studies for inclusion was determined using the PICOS framework (76). Full-text articles in languages other than the English language were excluded. Selection of studies for inclusion was determined using the PICOS framework (76). Full-text articles in languages other than the English language were excluded.

The economic searches were limited by date and include only publications since 2012 because the changes in the management of patients with AML in the last decade were believed likely to impact the HCRU and costs associated with AML. The searches were not limited by geographical location.

The economic SLR has two parts in line with the NICE single technology appraisal template i.e. a cost-effectiveness section and a cost and healthcare resource use (HCRU) section. Consequently, there are two sets of PICOS for the economic SLR.

The inclusion and exclusion criteria of the literature reviews are presented in Table 101 (cost-effectiveness) and Table 102 (HCRU).

Table 101. Eligibility criteria of the cost-effectiveness evidence search

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years old) with AML that is FLT3+	• Condition other than AML • Paediatric patients (<18 years old) • Non-human

Interventions/ Comparators	No limitations	None
Outcomes	Model structure and any health economic outcome, including (but not restricted to) QALYs, ICERs, LYG or costs	Studies not providing data on the specific outcomes of interest
Study design (s)	• Economic evaluations • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-consequence analysis • Cost-minimisation analysis • SLRs involving these study types**	• Case reports • Editorials, notes, comments
Limits	• Language: English only studies • Publication date: 2012 to date • Conference abstracts published after 2020 • Country: no limitations	• Non-English language studies • Conference abstracts prior to 2020

Notes: ** SLRs will be included at abstract review stage to search their reference lists for any missed studies and subsequently excluded during

Table 102. Eligibility criteria of cost and healthcare resource use evidence search

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years old) with AML that is *FLT3+*	• Condition other than AML • Paediatric patients (<18 years old) • Non-human
Interventions/ Comparators	No limitations	None
Outcomes of interest	• HCRU-related: • Resource use associated with the management of AML including but not limited to: • Hospitalisation (inpatient, outpatient, ER) • GPs, specialists, nurse visits • Diagnostic test • Procedures (e.g., stem cell transplant) • Management of treatment toxicity and complications • Cost related:	• Studies not providing data on the specific outcomes of interest

	• Direct medical costs (including health care and social care provision covering the cost of hospitalisation, outpatient follow-up, residential and day care, pharmaceutical interventions and laboratory testing) • Indirect costs (including loss of productivity and cost of caregiver's time)	
Study design of interest	• Cost/resource use • Resource use studies • Drug utilisation studies • Cost analysis • Economic evaluations reporting costs or resource use • SLRs involving these study types**	• Case reports • Editorials, notes, comments
Limits	• Language: English only studies • Publication date: 2012 to date • Conference abstracts published after 2020 • Country*: United Kingdom, other European Countries, Canada	• Non-English language studies • Conference abstracts prior to 2020

Notes: ** SLRs will be included at abstract review stage to search their reference lists for any missed studies and subsequently excluded during

J.1.3.2 Study selection process

The study selection process is detailed in Appendix H.1.5.2.

J.1.3.3 Results

J.1.3.3.1 Results of the cost-effectiveness search

In total 1,532 publications were screened for inclusion. This included a total of 715 references identified from electronic databases searches on the 9th of May 2023, (MEDLINE®: 63; Embase®: 539; Cochrane®: 31, Econlit®: 82) and an additional 817 publications from checking reference lists, trial registries and hand-searching of conference proceedings. No additional relevant studies were identified by cross-checking the references of the four SLRs identified in the database searches.

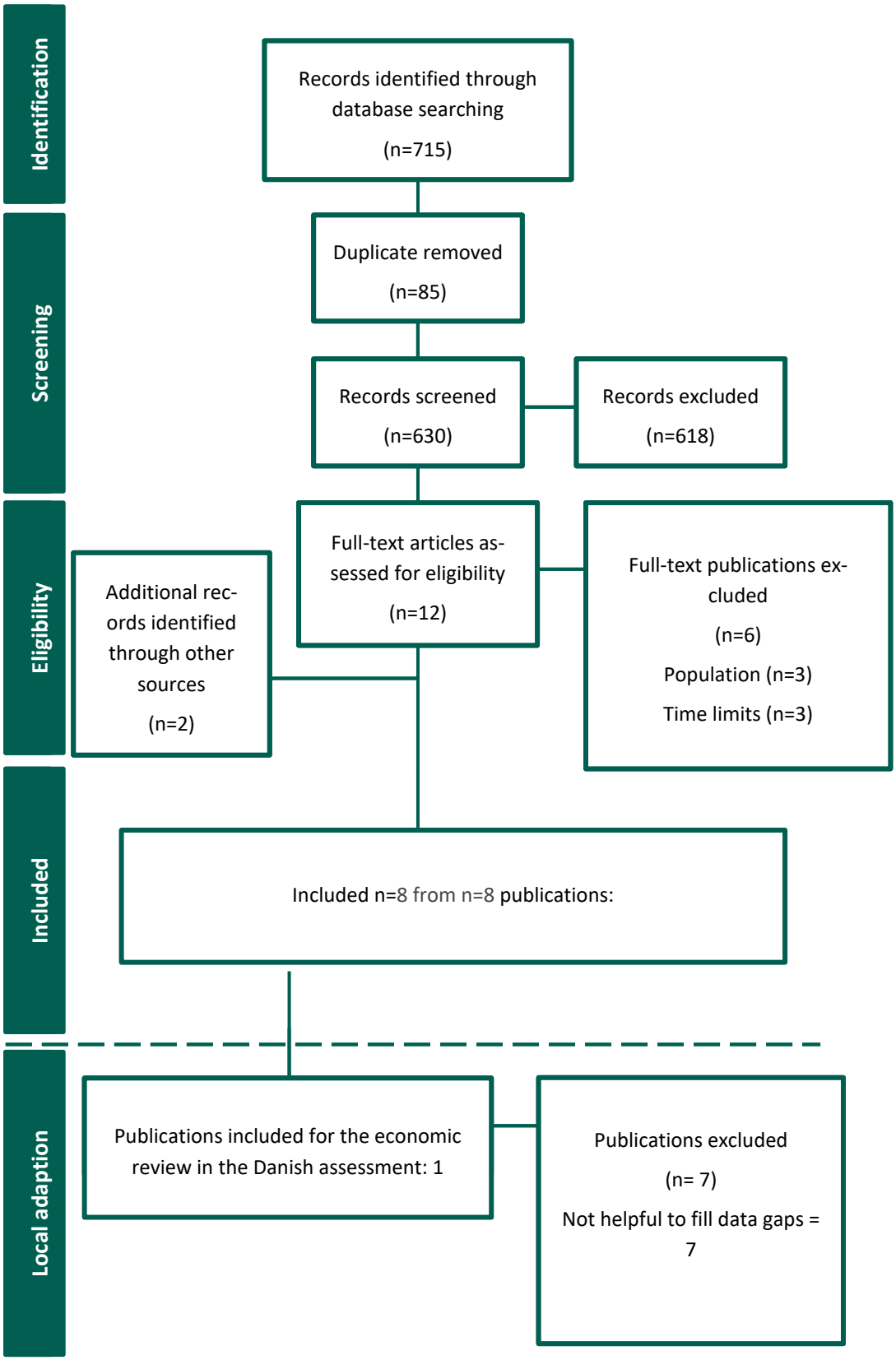
From the 715 publications identified via database search, 85 duplicate references were removed; 618 references were excluded after screening titles and abstracts against the eligibility criteria and 12 potentially relevant references were retrieved for full-text assessment. Of these 12 publications, six were included for data extraction, while 6 were excluded because the population was out of scope and for time limit.

From the 817 records identified via other methods, 2 NICE appraisals were identified via the hand search and included for extraction. This resulted in 8 study included.

In the local adaptation, 5 studies were excluded as these did not contain information for filling the data gaps, while 1 were included as source for the health economic model, namely NICE TA523.

The PRISMA diagram Figure 48 presents the results of the searches described above.

Figure 48 PRISMA flow diagram – economic SLR - economic evaluation studies



J.1.3.3.2 Results of the HCRU search

In total 1,534 publications were screened for inclusion. This included a total of 715 references identified from electronic databases searches on the 9th of May 2023, (Medline®: 63; Embase®: 539; Cochrane®: 31, EconLit®: 82) and an additional 819 publications from checking reference lists, trial registries and hand-searching of conference proceedings. Two additional relevant studies were identified by cross-checking the references of four SLRs identified in the database searches. Two relevant NICE appraisals were identified.

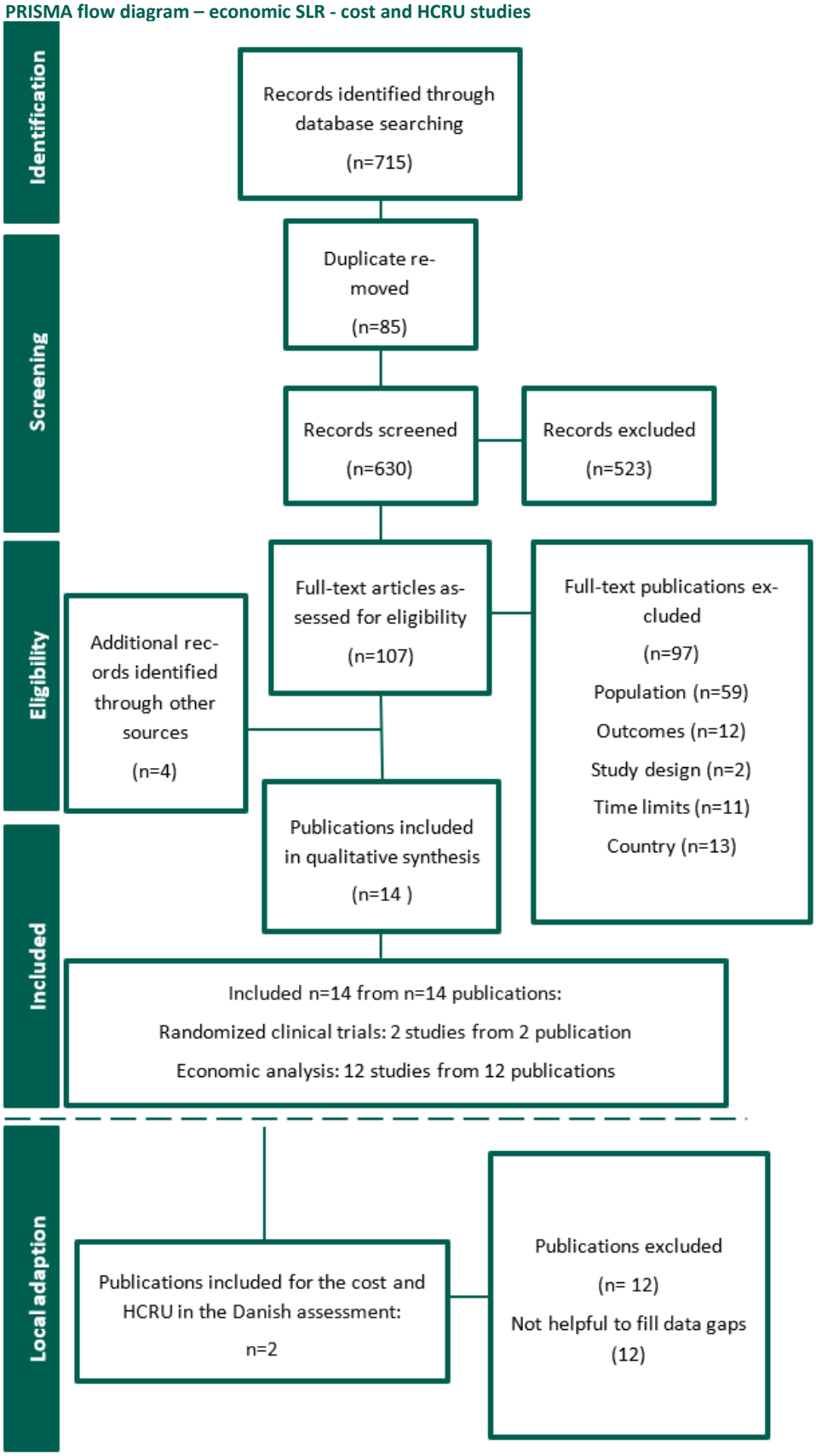
From the 715 publications identified via the database search, 85 duplicate references were removed; 523 references were excluded after screening titles and abstracts against the eligibility criteria and 107 potentially relevant references were retrieved for full-text assessment. Of these 107 publications, 10 (all full texts) were included for data extraction.

From the 819 records identified from the other methods, 2 NICE appraisals were identified via the hand search and the 2 studies identified from the cross-check of the bibliographies were included for data extraction. Therefore, in total 14 publications were included for data extraction.

In the local adaptation, 12 publications were excluded as did not contained data useful to fill the data gaps, while 2 were leveraged in the Danish health economic model, namely NICE TA523 and Perl and al., 2019.

The PRISMA diagram in Figure 49 presents the results of the searches described above.

Figure 49 PRISMA flow diagram – economic SLR - cost and HCRU studies



J.1.3.3.3 Overview of study design for studies included in the analyses

From the cost-effectiveness search 8 studies from 8 publications were identified and included for data extraction in the global SLR. In the locally adapted SLR, 1 study from 1 publication was included (these are highlighted in bold in Table 103). From the HCRU search 14 studies from 14 publications were identified and included in the global SLR. In the locally adapted SLR, 2 studies from 14 publications were included (these are highlighted in bold in Table 104). An overview of the studies included in the analysis is presented in Table 103 and Table 104.

Table 103 Overview of study design for studies included in the analyses (cost-effectiveness search)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))*	Primary outcome and follow-up period	Secondary outcome and follow-up period
Tremblay 2018 (98)	N/A	Partitioned-survival model with 8 health states	ND adult patients with *FLT3+* AML	Midostaurin + chemo Chemo	Costs LYs QALYs ICER	N/A
NICE TA523 (31)	**N/A**	**Partitioned-survival model with five health states**	**ND patients with *FLT3+* AML**	**Midostaurin+ Chemo** **Chemo**	**LYs** **QALY** **ICER**	**N/A**
Arenaza 2019 (101)	N/A	Partitioned-survival model with five health states	ND adult patients with *FLT3+* AML	Midostaurin + chemo Chemo	Costs LYs QALYs ICER	N/A
Tremblay 2020 (102)	N/A	Partitioned-survival model with 8 health states	ND adult patients with *FLT3+* AML	Midostaurin + chemo Chemo	Costs LYs QALYs ICER	N/A
Stein 2019 (103)	N/A	Partitioned-survival model with four health states	ND adult patients with *FLT3+* AML	Midostaurin + chemo Chemo	Costs LYs QALYs ICER	N/A
NICE TA642 (68)	N/A	Decision-tree structure followed by partitioned survival models	Adult patients with *FLT3+* R/R AML	Gilteritinib Salvage chemo	Cost QALY LY ICER	N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))*	Primary outcome and follow-up period	Secondary outcome and follow-up period
Pandya 2021 (104)	N/A	Decision tree structure followed by partitioned survival models	Adult patients with R/R *FLT3+* AML	Gilteritinib Salvage chemo BSC: palliative care	Costs LYs QALYs ICER	N/A
Imataki 2022 (117)	N/A	Markov model	Transplantation-Ineligible elderly Patients with *FLT3+* AML	Gilteritinib Quizartinib Chemo SCT	Daily drug cost CE ratio	N/A

Notes: *Sample size is not reported. Studies highlighted in **bold** are included in the locally adapted SLR.

Table 104 Overview of study design for studies included in the analyses (HCRU search)

Study/ID	Aim	Study design	Patient population	Intervention and comparator* (Sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Griffin 2021 (118)	N/A	HCRU	ND *FLT3+* AML	1,208	HCRU	N/A
Shah 2021 (119)	N/A	HCRU	ND *FLT3+* AML	218	HCRU	N/A
Larson 2021 (54)	N/A	Clinical trial with CRU outcomes	ND *FLT3+*AML	717	HCRU	N/A
Perl 2019 (57)	**N/A**	**Clinical trial with CRU outcomes**	**R/R *FLT3+* AML**	**371**	**HCRU**	**N/A**
Griffin 2019 (120)	N/A	HCRU	*FLT3+*AML	500	HCRU	N/A
Arenaza 2019 (101)	N/A	CEA	ND *FLT3+* AML	717	HCRU Cost	N/A
NICE TA523 (31)	**N/A**	**CEA**	**ND *FLT3+* AML**	**N/A**	**HCRU** **Cost**	**N/A**
Tremblay 2020 (102)	N/A	CEA	ND *FLT3+* AML	N/A	Cost	N/A
Tremblay 2018 (98)	N/A	CEA	ND *FLT3+* AML	N/A	HCRU Cost	N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator* (Sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Hernlund 2021 (121)	N/A	HCRU	ND *FLT3+* AML	298	HCRU Cost	N/A
NICE TA642 (68)	N/A	CEA	R/R *FLT3+* AML	N/A	HCRU Cost	N/A
Othman 2021 (122)	N/A	HCRU	R/R *FLT3+* AML	50	HCRU	N/A
Solana-Altabella 2021 (123)	N/A	HCRU	R/R *FLT3+* AML	38	HCRU	N/A
Bertoli 2020 (124)	N/A	HCRU	*FLT3+* AML	347	HCRU	N/A

Notes: *Intervention and comparator is not reported. Studies highlighted in **bold** are included in the locally adapted SLR.

J.1.4 Quality assessment

A limitation for the included studies is that there were relatively few available. Furthermore, they covered several countries which had significant differences in costs. Any biases that might have been in the study could therefore not be easily validated with alternative sources.

J.1.5 Unpublished data

No unpublished data was used as inputs of the economic model, with the exception of KOL opinion and assumptions.

Appendix K. Model structure and rationale

In Table 105 a comparison between the midostaurin model and the current model is provided, with rationale for the development of additional health states and changes of model type.

Table 105. Model structure rationale

Factor	Comparison	Justification
Model framework	**TA 523**: PSA **Current:** Semi Markov model	In the TA523 model, patients who failed to respond or relapsed after 1L moved to the relapse state, where they could only transition to HSCT or death, as achieving CR was not possible. The model assumed uniform HRQoL and costs for all patients in relapse and did not account for the benefits of 2L treatments, preventing patients from moving to CR. This limitation led the ERG to argue that the model underestimated the ICER. To address this, 2L treatment effects have been incorporated, and a CR2 state was added to differentiate between patients responding to 2L treatment and those who do not, in terms of costs, QALYs, and disease progression. A Markov model was deemed suitable to allow these adjustments.
Cure modelling	**TA 523**: A cure point of about 6.2 years (80 cycles in the model) was applied in the company submission **Current:** A cure point of three years was applied	In TA523, the ERG noted that the company's cure point was arbitrary, while clinical experts suggested that remission beyond 5 years indicated a cure (125). The committee concluded that allowing surviving patients with relapsed disease to enter a cured health state after 3 years was the most appropriate approach, aligning with the point where data showed a levelling-out effect. Similarly, in TA642, the committee deemed a cure point between 2 and 3 years plausible. (4). In the quizartinib model, 3 years was chosen as the cure point based on observed levelling-out effects, confirmed by UK clinical experts.
Health states	**TA 523**: Induction, CR, Relapse, HSCT, Death **Current:** Induction, CR1, HSCT 1L, post-HSCT maintenance 1L, post-HSCT relapse 1L, Refractory, Relapse 1L, CR2, HSCT 2L, post-HSCT maintenance 2L, Relapse 2L, Death	In TA523, the ERG highlighted that refractory patients were grouped with those who relapsed after achieving CR, making it impossible to distinguish between the two. Costs and HRQoL were assumed to be the same for both groups. In the quizartinib model, refractory and relapsed diseases are modelled as separate health states, allowing for distinct costs and utilities. Post-HSCT relapse is also included, with these patients placed in a separate state to prevent receiving a second HSCT.
HSCT Tunnel states	**TA 523:** HSCT tunnel states: HSCT treatment, HSCT recovery and post-HSCT recovery. **Current:**	The midostaurin model assumed that patients entering the HSCT state either remained in recovery or transitioned to death, overlooking the 25-40% relapse rate reported in the literature and the lower utility associated with post-HSCT relapse.

	HSCT tunnel states: HSCT and HSCT recovery.	The quizartinib model addresses this by including post-HSCT maintenance and HSCT relapse as separate states

In Table 106 the approach taken to derive each TP used in the economic model is summarised. While TP applied before failure of 1L treatments are treatment specific, if not assumed otherwise, TP in the health states following failure of 1L treatments are equal for quizartinib and midostaurin.

CR in the economic model is in line with the Q-F definition of CRc, which is the percentage of subjects achieving CR or CRi after induction. Refractory disease was defined as CR never achieved in the induction phase within a 42-day window from the start of the last induction cycle; or Blasts <5% if Auer-rod positive; or appearance of new or worsening extramedullary disease. TPs from the induction health state to CR1, refractory, and the death health state were calculated based on the proportion of patients who had CRc, refractory disease, and death events during the first and second induction rounds in the trial.

The time-variant transition probabilities (TPs) from CR1 to Relapse1 and Death were derived from the RFS and OS data from the Q-F (quizartinib) trial and the MAIC analysis (SC and midostaurin). These survival curves are detailed in section 8.1.1

For the CR1 to HSCT 1L transition, TPs were based on the proportion of patients receiving HSCT after complete response in the Q-F and RATIFY trials. In Q-F, consolidation options included chemotherapy followed by quizartinib, HSCT, or both. HSCT could be performed during consolidation for patients achieving CR or CRi, or after induction if criteria were met within three months of the continuation phase. In the RATIFY trial, HSCT was not mandated, and 57% of patients underwent transplant at some point, with 28.1% in the midostaurin group and 22.7% in the placebo group receiving transplant during CR1. To align with Q-F transplant timing (between 2 and 6 months), the model allowed transition to HSCT 1L over four cycles (cycle 2 to cycle 6). The TP for this transition was calibrated using MS Excel's 'Solver' add-in, ensuring the model's transplant rate matched the proportions observed in both Q-F and RATIFY. For the quizartinib and SC regimens, the target transplant rate from Q-F was [redacted]% for quizartinib ([redacted]/[redacted]) and [redacted]% for SC ([redacted]/[redacted]). For midostaurin, the target rate from RATIFY was 28.1%

Table 106. Sources and main assumptions for model's transitions

Transition		Source of data and method	
From	**To**	**quizartinib**	**midostaurin**
Induction (1st cycle)	Induction 1	Residual	
	CR1	Q-F MAIC adjusted quizartinib data. % of patients achieving CRc from induction within 28 days	OR for CR versus quizartinib from MAIC applied to quizartinib TP
	Refractory 1	Q-F MAIC adjusted quizartinib data. % of patients achieving refractory disease from induction within 28 days	Assumed = to quizartinib

	Death	Q-F MAIC adjusted quizartinib data. % of patients achieving death from induction within 28 days	Assumed = to quizartinib
Induction (2nd cycle)	Induction	All patients are assumed to transition from induction after the 2nd cycle	Assumed = to quizartinib
	CR1	Q-F MAIC adjusted quizartinib data. Proportion of patients achieving CRc from induction after day 29	OR for CR versus quizartinib from MAIC applied to quizartinib TP
	Refractory 1	Residual	
	Death	Q-F MAIC adjusted quizartinib data. Proportion of patients dying from induction after day 29	Assumed = to quizartinib
CR1	CR1	Residual	
	Relapse 1	Q-F MAIC adjusted quizartinib data. Time varying calculated based on extrapolation of RFS from CRc censored for HSCT	HR for CIR versus quizartinib from MAIC applied to quizartinib RFS curve
	HSCT	Q-F ITT quizartinib data (info for MAIC adjusted population not available).	Stone et al data
	Death	Time varying calculated based on extrapolation of Death from CRc censored for HSCT	HR for OS versus quizartinib from MAIC applied to quizartinib OS curve
Post HSCT-maintenance (1 and 2L)	Relapse 1 and 2	Q-F ITT quizartinib data (info for MAIC adjusted population not available). % of patients who had a HSCT who relapsed	Assumed as placebo in Q-F ITT data
		For 2 L , assumed 50% higher than the 1L placebo arm for both quizartinib and midostaurin	
HSCT states	Death	Number of deaths from Styczynski et al, 2019 Cohort 2	
Refractory	Refractory	Residual	
	CR2	ADMIRAL trial (Perl et al., 2019): Proportion of patients with primary refractory AML achieved a CR/CRh across gilterinib and salvage chemotherapy arms, responding over 1.97 months (weighted average time to CRc in gilteritinib and salvage chemotherapy	
	Death	ADMIRAL trial (Perl et al., 2019): 60-day mortality weighted by trial arm, assumed to be time-invariant and adjusted to transition probability for 28-day cycle length	
Relapse 1	Relapse 1	Residual	

	CR2	Proportion of patients across gilterinib and salvage chemotherapy arm responding over 1.96 months (weighted average time to CRc in gilteritinib in salvage chemotherapy arms
	Death	Assumed = to refractory
CR2	CR2	Residual
	Relapse 2	ADMIRAL follow up (Perl et al., 2022). The 2-year cumulative relapse rate in gilteritinib treated patients who achieved a best response of CR was 56.2% A meaningful assessment of cumulative relapse rates in the SC arm could not be performed because bone marrow samples were only collected up to the end of treatment, and nearly all patients in the SC arm had discontinued treatment after ≤2 treatment cycle
	HSCT 2L	ADMIRAL follow up (Perl et al., 2022) proportion of patients in the safety analysis set who underwent a HSCT
	Death	ADMIRAL follow up (Perl et al., 2022). One year mortality weighted by trial arm, assumed to be time-invariant and adjusted to 28-day cycle length
Relapse 2	Relapse 2	Residual
	Death	Assumed = to relapse 1

Appendix L. ITT population data

In this appendix, clinical data for the ITT population is reported. This includes:

- Baseline population characteristics
- Efficacy endpoints
- Safety data
- Inputs used in the cost effectiveness model to conduct the scenario based on Q-F ITT data (Naïve scenario)

L.1 Baseline characteristics of Q-F ITT population

Baseline characteristics of the Q-F ITT population are presented in Table 107.

Table 107 Baseline characteristics of patients in Q-F (ITT population)

	Q-F (ITT)	
	Quizartinib (N = 268)	**Placebo (N = 271)**
Median age (range), years	56.0 (23-75)	56.0 (20-75)
Sex, female, n (%)	144 (53.7)	150 (55.4)
Race, n (%)		
White	159 (59.3)	163 (60.1)
Other	27 (10.1)	24 (8.9)
Asian	80 (29.9)	78 (28.8)
Black or African American	2 (0.7)	5 (1.8)
Subtype of *FLT3* mutation with an allelic ratio cut-off of 0.7, n (%)		
TKD	0 (0)	0 (0)
ITD with a low ratio (≤0.7)	[redacted]	[redacted]
ITD with a high ratio (>0.7)	[redacted]	[redacted]
Subtype of *FLT3* mutation with an allelic ratio cut-off of 0.5, n (%)		
TKD	0 (0)	0 (0)
ITD with low ratio (≤0.5)	[redacted]	[redacted]
ITD with high ratio (>0.5)	[redacted]	[redacted]
Platelet counts (10^3/µL)*, median (range)	[redacted]	[redacted]
Cytogenetic risk, n (%)		
Favourable	14 (5.2)	19 (7.0)
Intermediate	197 (73.5)	193 (71.2)
Adverse	19 (7.1)	27 (10.0)
Unknown	38 (14.2)	21 (11.4)

Absolute neutrophil count per mm^3, median (range)	[redacted]	[redacted]
White blood cell count (10^3/µL)		
<40 × 10^9/L	135 (50.4)	137 (50.6)
≥40 × 10^9/L	133 (49.6)	134 (49.4)
Median (10^9/L)	N/A	N/A
Bone marrow blasts, median (range)	[redacted]	[redacted]
NPM1 mutation, n (%)	142 (53.0)	140 (51.7)

Source: Daiichi Sankyo, 2023, table 3 (7); Daiichi Sankyo, 2022, Table 7.5 (8).

As outlined in Table 107, patients in the quizartinib arm and placebo arm were similar.

L.2 Efficacy endpoints

All endpoints presented derived from the 13 August 2021 data cut off. If not otherwise specified, for the Q-F endpoints, medians time to event and event rates were derived from KM estimates, CI for medians was computed using the Brookmeyer-Crowley method, HR were derived from Cox proportional hazards model and two-sided p-value from log-rank test.

Treatment discontinuation

Discontinuation was similar in both groups (quizartinib: [redacted]%, placebo: [redacted]%). The key reasons included refractory disease (15.5%, 26.1%), relapse (16.6%, 24.3%) and AE (21.9% vs. 8.6%). Other reasons like subject decisions, investigator decisions, and non-protocol therapy were reported at lower rates in both groups (63).

L.2.1 Overall survival

In Table 108, the results of the OS per IRC assessment are presented. In combination with SC, treatment with quizartinib resulted in a statistically significant OS benefit compared with placebo (HR 0.776 (0.615, 0.979), p-value = 0.0324), corresponding to a 22.4% relative risk reduction of death in favour of the quizartinib arm. The median OS was 31.9 (21.0, NE) months in the quizartinib arm compared with 15.1 (13.2, 26.2) months in the placebo arm. The OS rate at all time points (from 6 months to 48 months) was higher in the quizartinib arm compared to in the placebo arm.

Table 108 Overall survival (ITT population)

Estimate	Quizartinib (n=268)	Placebo (n=271)
Subjects (%) with events (deaths)	133 (49.6)	158 (58.3)
Median OS months (95% CI)	31.9 (21.0, NE)	15.1 (13.2, 26.2)
HR (relative to placebo), 95% CI[b]	0.776 (0.615, 0.979)	Reference
p-value (2-sided)[b]	0.0324	
6 months OS rate, % (95% CI)	[redacted]	[redacted]
12 months OS rate, % (95% CI)	67.4 (61.3, 72.7)	57.7 (51.6, 63.4)
24 months OS rate, % (95% CI)	54.7 (48.4, 60.5)	44.7 (38.7, 50.6)
36 months OS rate, % (95% CI)	49.9 (43.7, 55.9)	41.1 (35.0, 47.0)
48 months OS rate, % (95% CI)	48.4 (41.9, 54.5)	37.0 (29.8, 44.2)

Notes: [b] Stratification factors in the Cox regression analysis include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old), and WBC count at the time of diagnosis of AML (<40 x 10^9/L, ≥40 x 10^9/L).
Source: Daiichi Sankyo Inc., 2022, table 8.1 (8).

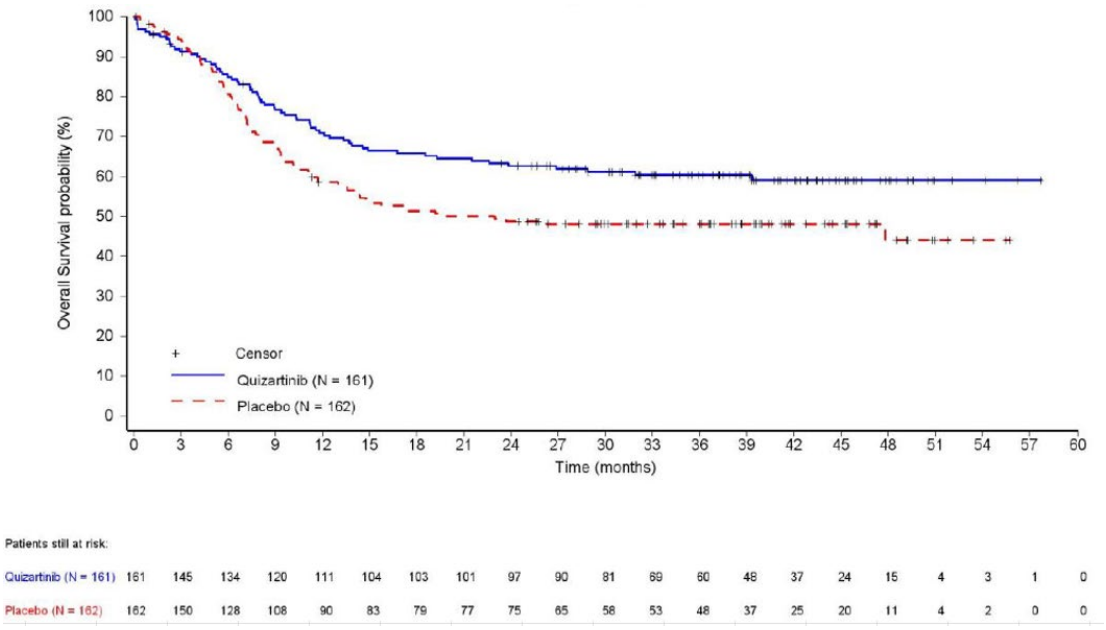


Figure 4 shows a Kaplan-Meier plot of OS. The curves cross at approximately 5 months, probably due to infections as observed also in the RATIFY trial. After that, there is a clear separation between the quizartinib arm and the placebo arm favouring quizartinib.

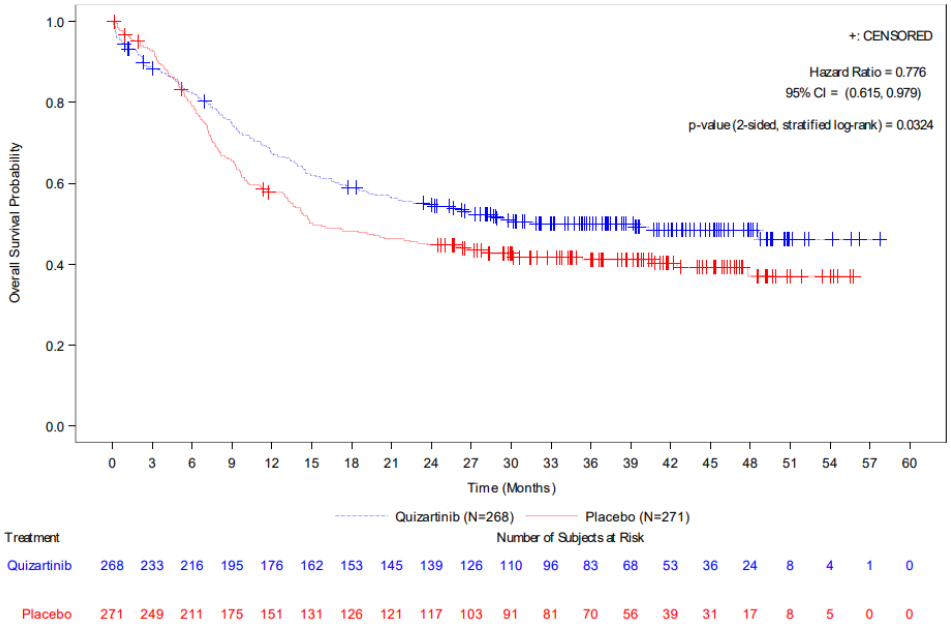


Figure 50 Kaplan-Meier plot of overall survival (ITT analysis set)

Note: Based on stratified Cox proportional hazard model and stratified log-rank test.
Source: Daiichi Sankyo Inc., 2022, figure 8.1 (8).

L.2.2 Event-free survival

Table 109 presents the results of the EFS endpoints. The analysis of EFS per IRC assessment was based on lack of induction treatment success (i.e., not having CR) during a 42-day period from the start of the last induction cycle (as defined in US FDA AML guidance) (126). The median EFS was 0.03 months (0.03, 0.95) in the quizartinib arm and 0.71 months (0.03, 3.42) in the placebo arm. There was no statistically significant difference between the two arms. Because the analysis of EFS was not statistically significant, formal hierarchical testing was not continued. Sensitivity and supplementary analyses of EFS used different definitions, such as not having CRc (original protocol definition) or not having CR by the end of induction (including the optional second cycle) until blood count recovery up to day 56. These alternative definitions have not been included in this application to align with the definition used in the US FDA AML guidance (126) and in the EPAR. (126) and in the EPAR. These alternative definitions have not been included in this application to align with the definition used in the US FDA AML guidance (126) and in the European Public Assessment report (127).

Table 109 Event free survival (with a 42-day window) (ITT population)

Estimate	Quizartinib (n=268)	Placebo (n=271)
Subjects (%) with events	198 (73.9)	213 (78.6)
Median EFS months (95% CI)[a]	0.03 (0.03, 0.95)	0.71 (0.03-3.42)
HR (relative to placebo), 95% CI[b]	0.916 (0.754, 1.114)	Reference
p-value (2-sided)[b]	0.2371	
6 months EFS rate, % (95% CI) [c]	[redacted]	[redacted]
12 months EFS rate, % (95% CI) [c]	[redacted]	[redacted]
18 months EFS rate, % (95% CI) [c]	[redacted]	[redacted]
24 months EFS rate, % (95% CI) [c]	[redacted]	[redacted]
30 months EFS rate, % (95% CI) [c]	[redacted]	[redacted]
36 months EFS rate, % (95% CI) [c]	[redacted]	[redacted]

Notes: [b] Stratification factors in the Cox regression analysis include region (North America, Europe, Asia/other regions), age (<60, ≥60 years old), and WBC count at the time of diagnosis of AML (<40 x 10^9/L, ≥40 x 10^9/L).
Source: Daiichi Sankyo Inc., 2022, table 8.4 (8).

The EFS curves are shown in Figure 51 indicating a minor separation between the quizartinib arm and the placebo arm favouring quizartinib.

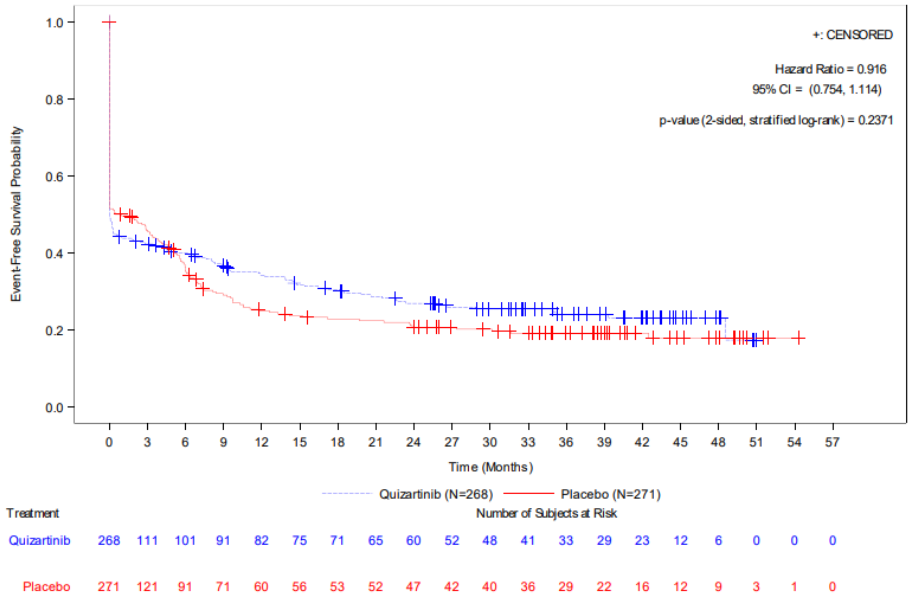


Figure 51 KM of event-free survival (with a 42-day window)

Note: Based on stratified Cox proportional hazard model and stratified log-rank test.
Source: Daiichi Sankyo Inc., 2022, figure 8.4 (8).

L.2.3 Complete remission endpoints

Table 110 provides an overview of the results of analyses of CR endpoints. Numerically higher CRc rates were observed in the quizartinib arm (71.6%) compared to the placebo arm (64.9%) and were primarily driven by higher rates of CRi in the quizartinib arm (16.8%) than in the placebo arm (9.6%).

Table 110 CR endpoints– (ITT analysis set)

Estimate	Quizartinib (n=268) n (%), (95% CI[a])	Placebo (n=271) n (%), (95% CI[a])	Analysis (quizartinib vs. placebo) p-value[c]
CR	147 (54.9), (48.7, 60.9)	150 (55.4), (49.2, 61.4)	[redacted]
CRc (CR + CRi)	192 (71.6), (65.8, 77.0)	176 (64.9), (58.9, 70.6)	[redacted]
CRi[b]	45 (16.8), (12.5, 21.8)	26 (9.6), (6.4, 13.7)	[redacted]

Notes: [a] Based on the Clopper-Pearson method. [b] CRi was not specified as a secondary endpoint but is included for completeness. [c] Based on the Cochran-Mantel-Haenszel test adjusted for stratification factors: region (North America, Europe, Asia/Other Regions), age (<60, ≥60 years old), and white blood cell count at the time of diagnosis of AML ($<40\times10^9$/L, $\geq40\times10^9$/L).
Source: Daiichi Sankyo Inc., 2022, table 8.7 and table 14.2.3 (8).

L.2.4 Cumulative incidence of relapse in the Q-F ITT population

A post-hoc analysis was performed to analyse the CIR in all subjects who achieved a CR in the induction phase treating death prior to relapse as a competing risk (IRC assessment). The CIR rates were numerically lower in the quizartinib arm than the placebo arm, as shown in **Table 111**.

Table 111 CIR in patients who achieved CR in induction (ITT analysis set)

Estimate	Quizartinib (n=142) n (%)	Placebo (n=150) n (%),
Subjects with event (relapse)	44 (29.9)	63 (42.0)
Subjects with competing risk (death)	[redacted]	[redacted]
Subjects without events (censored)	[redacted]	[redacted]
CIR rate (%, 95% CI[a]) at:		
12 months	18.7 (12.7, 25.6)	34.9 (27.1, 42.7)
24 months	31.2 (23.5, 39.2)	43.3 (34.9, 51.3)
36 months	33.8 (25.5, 42.2)	45.1 (36.5, 53.2)

Notes: [a] Estimated using the cumulative incidence function.
Source: Daiichi Sankyo Inc., 2022, table 8.9 (8).

The CIR curves are shown in Figure 52 indicating a clear separation between the quizartinib arm and the placebo arm favouring quizartinib. Both curves appear to plateau after approximately 24 months.

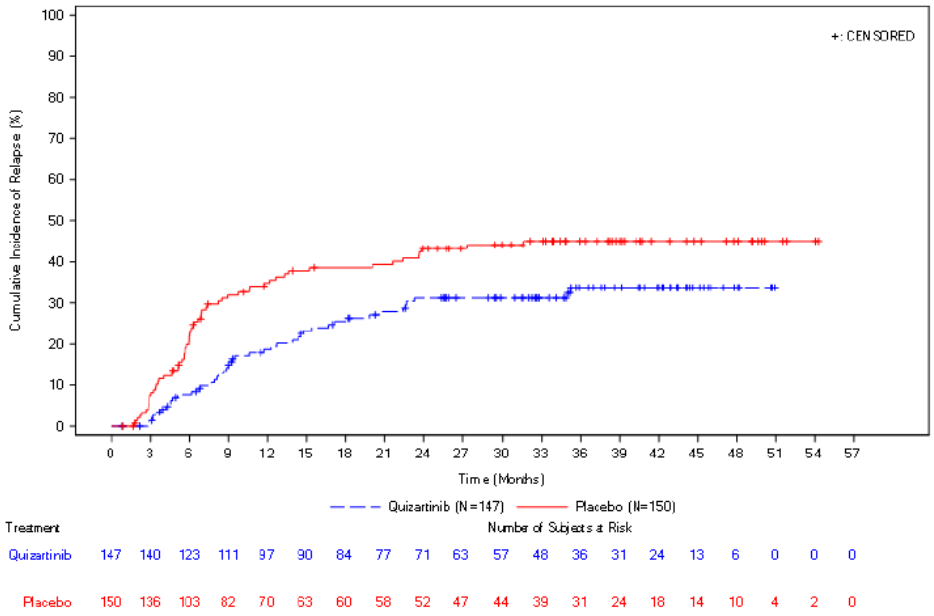


Figure 52 KM of CIR for subjects achieving CR in induction (ITT analysis set)

Source: Daiichi Sankyo Inc., 2022, figure 8.9 (8).

L.2.5 Relapse-free survival for subjects achieving CRc in induction

RFS was included in QuANTUM-First as an exploratory endpoint. The median RFS in subjects achieving CRc during the induction phase was 28.5 (18.5 to NE) months in the quizartinib arm and 12.6 (9.7 to 23.7) months in the placebo arm (Table 112). The HR using an unstratified Cox model was 0.733 (0.554 to 0.969). The corresponding KM plot is presented in Figure 6.

Table 112 RFS for subjects achieving CRc in induction (ITT analysis set)

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

Notes: [a] Unstratified Cox regression analysis.
Sources: Daiichi Sankyo, 2022, table 8.10 (8); Erba et al., 2023 (10).

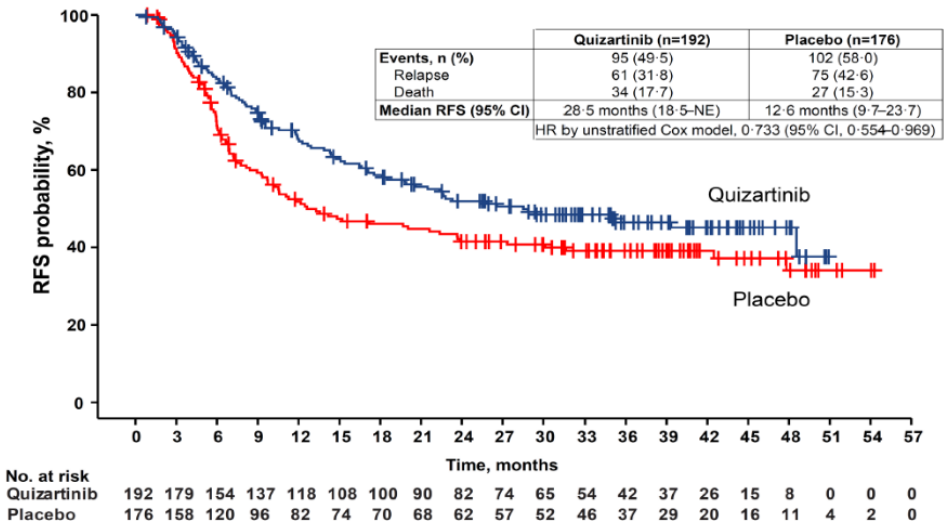


Figure 53 KM of RFS for subjects who achieved CRc in induction (ITT analysis set)

Source: Erba et al., 2023 (10).

An additional analysis of RFS was completed which defined RFS as for patients who achieved CR (rather than CRc as in the protocol definition of RFS) during induction, until

the date of documented relapse or death from any cause, whichever occurred first. The results of this endpoint are described in Table 61 for the ITT population.

L.2.6 Duration of complete remission in the Q-F ITT population

Median DUR was included in Q-F as an exploratory endpoint. Median DUR was 38.6 (21.9 to NE) months for quizartinib and 12.4 (8.8 to 22.7) months for placebo (Table 113). There was a clear and sustained separation of the curves for up to three years as seen in Figure 54.

Table 113. Analysis of DUR- (ITT Analysis Set)

Statistics	Quizartinib (N=268)	Placebo (N=271)
Subjects with CR, n (%)	147 (54.9)	150 (55.4)
Median duration of CR (months) (95% CI)	38.6 (21.9, NE)	12.4 (8.8, 22.7)
Hazard ratio (95% CI)	0.621 (0.451, 0.857)	
DoCR rate, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]

Sources: Daiichi Sankyo, 2022, table 8.13 (8); Erba et al., 2023 (10).

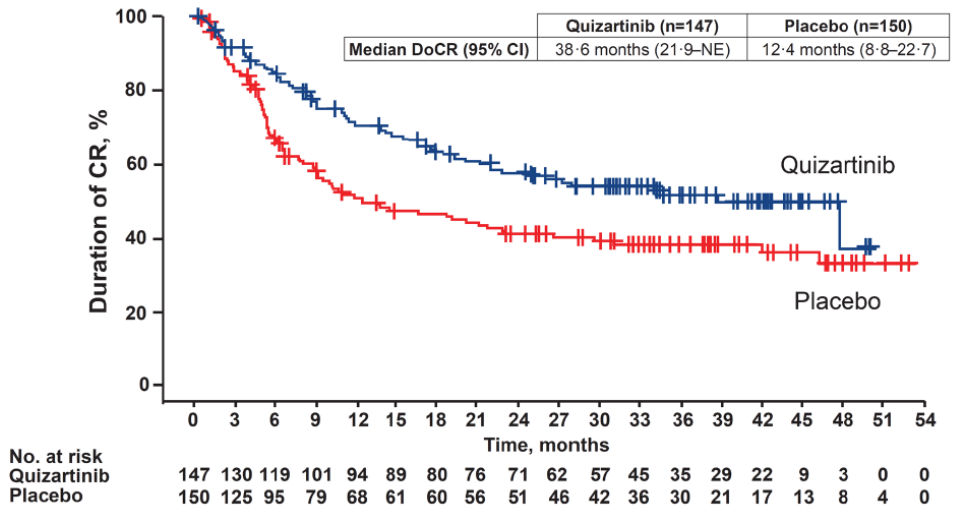


Figure 54 KM plot for DUR in patients who achieved CR during induction (ITT Analysis set)

Source: Erba et al., 2023 (10).

L.2.7 Transplantation rate in the Q-F ITT population

Transplantation rate was included in QuANTUM-First as an exploratory endpoint. A total of 102 (38.1%) subjects in the quizartinib arm and 91 (33.6%) subjects in the placebo arm underwent protocol-specified HSCT[1]. A further 15.6% and 13.6% of subjects received non-protocol specified HSCT in the quizartinib and placebo arms respectively (Table 114).

Table 114. HSCT rate (ITT analysis set)

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

Notes: [a] Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens). [b] Based on the Clopper-Pearson method. [c] Any HSCT performed for other reasons will be considered non-protocol-specified AML therapy, and the subject will be discontinued from quizartinib or placebo but will continue to be followed for outcome data.
Sourcess: Daiichi Sankyo, 2022 (8); Erba et al., 2023 (10).

15.1.1.1 Time to discontinuation

Time to discontinuation is an additional endpoint included in Q-F. Median time to treatment discontinuation was [redacted] months ([redacted], [redacted]) for quizartinib and [redacted] months ([redacted], [redacted]) for placebo. The HR resulting from the stratified Cox proportional hazards model was [redacted] ([redacted], [redacted]).

[redacted]

Figure 55. KM plot for time to discontinuation (ITT analysis set)

Sourcess: Daiichi Sankyo, 2022 (8).

L.3 Safety

Table 115 provides an overview of safety events in Q-F ITT population and RATIFY. Within Q-F, the safety events were generally similar, although more participants in the quizartinib arm had ≥ 1 SAE, a dose reduction, and discontinued treatment due to AEs compared to participants in the placebo arm. Within RATIFY, the safety events were similar across

treatment arms. However, only limited safety data were available for RATIFY. Compared to RATIFY, a higher percentage of subjects in Q-F had at least one AE and discontinued treatment due to AEs.

Table 115 Overview of safety events (Q-F (13-08-2021) and RATIFY (July 2016))

	Q-F Quizartinib (N=265)	Q-F Placebo (N=268)	RATIFY Midostaurin (N=360)	RATIFY Placebo (N=357)
Number of AEs, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥1 AEs, n (%)	[redacted]	[redacted]	321/355[Ω] (90.42)[‡]	324/354 [Ω] (91.53)[‡]
Number of SAEs*, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 SAEs*, n (%)	[redacted]	[redacted]	157/355[Ω] (44.23)	154/354[Ω] (43.50)
Number of CTCAE grade ≥ 3 events, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	[redacted]	[redacted]	N/A	N/A
Number of adverse reactions, n	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	264 (99.6)[¥]	265 (98.9)[¥]	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	212 (80.0%)	219 (81.7%)	N/A	N/A
Number and proportion of patients who discontinue	58 (21.9)	23 (8.6)	11 (3.1)	5 (1.3)[π]

	Q-F Quizartinib (N=265)	Q-F Placebo (N=268)	RATIFY Midostaurin (N=360)	RATIFY Placebo (N=357)
treatment due to AEs, n (%)				

Notes: *A SAE is an event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect. [§] CTCAE v. 5.0 must be used if available. [¥] Number and proportion with treatment-related AE. [Ω] Number affect / number at risk. [ǂ] Not including SAEs. a: median treatment duration of trial treatment = 10.71 weeks in Q-F. b: median treatment duration of trial treatment = 3 months in RATIFY (2). Notes: *A SAE is an event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect. [§] CTCAE v. 5.0 must be used if available. [¥] Number and proportion with treatment-related AE. [Ω] Number affect / number at risk. [ǂ] Not including SAEs. a: median treatment duration of trial treatment = 10.71 weeks in Q-F. b: median treatment duration of trial treatment = 3 months in RATIFY (2).
Source: Daiichi Sankyo, 2022, table 10.1, table 10.4, table 14.3.1.5.1, and table 14.3.1.5.2 (8) European Medicines Agency, 2017 (69), ClinicalTrials.gov, 2008 (9)

Table 116 provides an overview of SAEs in Q-F (8) and RATIFY (9). SAEs were similar both within the two treatment arms of Q-F and within the two treatment arms of RATIFY. Overall, a lower percentage of subjects in Q-F experienced SAEs compared to subjects in RATIFY. For instance, less subjects in Q-F experienced febrile neutropenia, vomiting, decreased neutrophil count, and decreased platelet count compared to subjects in RATIFY. In RATIFY and Q-F, there was a discrepancy in the classification of safety events. Several SAEs in RATIFY were classified as TEAEs or AEs in Q-F, which is indicated in Table 116 with [Ω] or [ǂ], respectively. In Appendix E, treatment-emergent SAEs in ≥1% of subjects in the Q-F ITT population are presented.

Table 116 Serious adverse events (Q-F [13-08-2021] and RATIFY [July 2016])

Serious adverse events	Quizartinib (N=265)		Placebo (N=268)		Midostaurin (N=355)		Placebo (N=354)	
	No. with SAEs	No. of SAEs	No. with SAEs	No. of SAEs	No. with SAEs	No. of SAEs	No. with SAEs	No. of SAEs
Pneumonia, n (%)	17 (6.4)	N/A	15 (5.6)	N/A	25 (7.04)	32	35 (9.89)	39
Sepsis, n (%)	10 (3.8)	N/A	15 (5.6)	N/A	23 (6.48)	27	16 (4.52)	17
Febrile neutropenia, n (%)	30 (11.3)	N/A	22 (8.2)	N/A	105 (29.58)	144	110 (31.07)	152
Haemoglobin decreased, n (%)	N/A	N/A	N/A	N/A	154 (43.38)	237	148 (41.81)	230
Diarrhoea, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	89 (25.07)	111	89 (25.14)	108
Ear, nose, and throat examination abnormal, n (%)	N/A	N/A	N/A	N/A	40 (11.27)	52	42 (11.86)	54
Nausea, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	98 (27.61)	149	91 (25.71)	126
Vomiting, n (%)	2 (0.8)	N/A	2 (0.7)	N/A	70 (19.72)	101	65 (18.36)	86
Fatigue, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	95 (26.76)	136	98 (27.68)	130
Fever, n (%)	N/A	N/A	N/A	N/A	34 (9.58)	38	33 (9.32)	38
Pain, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	14 (3.94)	17	18 (5.08)	24
Catheter site infection (Q-F)/Catheter related infection (RATIFY), n (%)	1 (0.4)	N/A	1 (0.4)	N/A	29 (8.17)	39	21 (5.93)	26
Infection, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	30 (8.45)	41	26 (7.34)	33
Alanine aminotransferase increased, n (%)	0	N/A	2 (0.7)	N/A	35 (9.86)	41	35 (9.89)	41
Alkaline phosphatase increased, n (%)	1 (0.4)	N/A	1 (0.4)	N/A	8 (2.25)	8	20 (5.65)	24
Aspartate aminotransferase increased, n (%)	0	N/A	1 (0.4)	N/A	30 (8.45)	33	29 (8.19)	32
Blood bilirubin increased, n (%)	1 (0.4)	N/A	1 (0.4)	N/A	25 (7.04)	32	36 (10.17)	42

Electrocardiogram QT prolonged (Q-F)/Electro-cardiogram QTc interval prolonged (RATIFY), n (%)	1 (0.4)	N/A	1 (0.4)	N/A	17 (4.79)	22	19 (5.37)	22
Gamma-glutamyltransferase increased, n (%)	1 (0.4)	N/A	1 (0.4)	N/A	19 (5.35)	25	22 (6.21)	32
Laboratory test abnormal, n (%)	N/A	N/A	N/A	N/A	18 (5.07)	33	28 (7.91)	47
Leukocyte count decreased, n (%)	N/A	N/A	N/A	N/A	41 (11.55)	66	47 (13.28)	78
Lymphocyte count decreased, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	22 (6.20)	30	36 (10.17)	56
Neutrophil count decreased, n (%)	4 (1.5)	N/A	0	N/A	145 (40.85)	227	146 (41.24)	224
Platelet count decreased, n (%)	1 (0.4)	N/A	1 (0.4)	N/A	155 (43.66)	239	146 (41.24)	227
Anorexia, n (%)	N/A	N/A	N/A	N/A	21 (5.92)	30	26 (7.34)	29
Blood glucose increased, n (%)	N/A[‡]	N/A	N/A[‡]	N/A	17 (4.79)	23	22 (6.21)	31
Serum albumin decreased, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	19 (5.35)	28	22 (6.21)	26
Serum calcium decreased, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	20 (5.63)	25	26 (7.34)	30
Serum potassium decreased, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	31 (8.73)	37	47 (13.28)	53
Serum sodium decreased, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	20 (5.63)	22	20 (5.65)	22
Dizziness, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	19 (5.35)	23	20 (5.65)	25
Headache, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	41 (11.55)	54	42 (11.86)	63
Cough, n (%)	1 (0.4)	N/A	0	N/A	17 (4.79)	21	19 (5.37)	20
Dyspnoea, n (%)	1 (0.4)	N/A	1 (0.4)	N/A	20 (5.63)	22	24 (6.78)	24
Epistaxis, n (%)	1 (0.4)	N/A	0	N/A	24 (6.76)	26	22 (6.21)	24
Pneumonitis, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	27 (7.61)	28	17 (4.80)	19
Petechiae, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	35 (9.86)	45	34 (9.60)	52
Rash desquamating, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	59 (16.62)	70	66 (18.64)	71
Skin disorder, n (%)	N/A[‡]	N/A	N/A[‡]	N/A	23 (6.48)	28	23 (6.50)	30

Hypotension, n (%)	N/A[Ω]	N/A	N/A[Ω]	N/A	25 (7.04)	26	19 (5.37)	22

Notes: [Ω] Defined as a TEAE in Q-F and not a SAE. [ǂ] Defined as an AE in Q-F and not a SAE. * A SAE is an event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect.
Source: Daiichi Sankyo, 2022, table 14.3.2.7 (8); ClinicalTrials.gov, 2008 (9).

L.4 Cost effectiveness analysis inputs

In this section the ITT data used to conduct the "naïve scenario" is described, as opposed to the Q-F subgroup younger than 60 used in the base case. Data include patients' characteristics as described in Section L.1, the TP, AE frequency and HRQoL. The extrapolations for Relapse and Death from CRc are presented in Appendix D.

L.4.1 Transition probabilities

The constant TP based on the ITT population are described in Table 117.

Table 117 Constant TP (1L – ITT population) used in the "Naïve scenario"

Transition (from to)	TPs(%) Quizartinib	midostaurin	Description of method and Reference
Induction 1 to Induction 1	Residual	Residual	-
Induction 1 to First CR	[redacted]	[redacted]	quizartinib: [redacted] of [redacted] patients had CRc within 28 days midostaurin: Applied CR OR vs quizartinib (1/0.92)
Induction 1 to Refractory	[redacted]	[redacted]	quizartinib: [redacted] of [redacted] patients had refractory disease within 28 days midostaurin assumed =quizartinib
Induction 1 to Dead	[redacted]	[redacted]	quizartinib: [redacted] of [redacted] patients died within 28 days midostaurin assumed =quizartinib
Induction 2 to Induction	[redacted]	[redacted]	All patients which require longer than 29 days to transition are moved out of induction at this cycle
Induction 2 to First CR	[redacted]	[redacted]	quizartinib: [redacted] patients remaining in induction after cycle 2, [redacted] achieved CRc midostaurin: Applied CR OR vs quizartinib (1/0.92)
Induction 2 to Refractory	Residual	Residual	-
Induction 2 to Dead	[redacted]	[redacted]	quizartinib: [redacted] patients remaining in induction in cycle 2, [redacted] died midostaurin assumed =quizartinib
First CR to First CR	Residual	Residual	-
First CR to 1L Relapse	Time-varying	Time-varying	quizartinib: Time to relapse from CRc censored for HSCT extrapolated midostaurin: CIR HR applied to quizartinib curve (1/0.42)
First CR to HSCT	[redacted]	[redacted]	Quizartinib: [redacted] patients with protocol specified HSCT after CRc out of 268

			midostaurin: Stone et al., 2017. Transplantation was performed during the first complete remission in [redacted]% of the patients in the midostaurin group. The TP were back calculated to ensure the sum of transplant rate in the patients' distribution equal to the targeted transplant rate.
First CR to Dead (Time-varying)	Time-varying	Time-varying	quizartinib: Time to death from CRc censored for HSCT extrapolated midostaurin: OS HR applied to quizartinib curve (1/0.82)
1L HSCT post recovery to relapse	[redacted]	[redacted]	quizartinib: [redacted] of [redacted] patients who had HSCT relapsed over an average length of [redacted] days, midostaurin: assumed = to SC in Q-F: [redacted] of [redacted] over a length of [redacted]

L.4.2 AE

Table 118 describes the AEs of grade ≥3 occurring with an incidence of ≥5% in the Q-F ITT population included in the analysis.

Table 118 Adverse events used in the health economic model

Adverse events	quizartinib	SC	Midostaurin	Source and Justification
Anaemia	5.7%	5.2%	92.7%	For quizartinib, grade ≥3 treatment-emergent AES that occurred in ≥ 5% of patients in Q-F trial For midostaurin, grade 3, 4 or 5 AEs that occurred in ≥ 5% of patients in midostaurin arm in RATIFY reported in Stone et al., 2017
Diarrhoea	3.8%	3.7%	15.8%	
Fatigue	0.4%	0.0%	9.0%	
Febrile neutropenia	43.8%	41.0%	81.7%	
Hyperbilirubinemia	[redacted]	[redacted]	7.0%	
Hypocalcaemia	0.8%	3.0%	6.8%	
Hypokalaemia	18.9%	16.4%	13.8%	
Hyponatraemia	[redacted]	[redacted]	8.7%	
Hypophosphataemia	6.8%	6.0%	5.4%	
Increased alanine aminotransferase	4.5%	4.9%	12.7%	
Infection	[redacted]	[redacted]	52.4%	
Leukopenia	[redacted]	[redacted]	26.2%	
Lymphopenia	[redacted]	[redacted]	19.2%	
Mucositis or stomatitis	4.5%	3.0%	6.2%	
Nausea	1.5%	1.9%	5.6%	
Neutropenia	18.1%	8.6%	95.2%	
Pain	[redacted]	[redacted]	13.2%	
Pneumonitis or pulmonary infiltrates	[redacted]	[redacted]	7.9%	

Adverse events	quizartinib	SC	Midostaurin	Source and Justification
Rash or desquamation	3.0%	1.1%	14.1%	
Thrombocytopenia	7.9%	-	97.5%	
Neutrophil count decreased	8.7%	-	0.0%	
Sepsis	5.7%	-	0.0%	
Gamma-glutamyl transferase increased	[redacted]	-	0.0%	
Platelet count decreased	[redacted]	-	0.0%	
Hypertension	4.9%	-	0.0%	
GVHD	55.9%	47.3%	39.0%	

Source: Daiichi Sankyo, 2022 (8); Stone et al. 2017 (2).Source: Daiichi Sankyo, 2022 (8); Stone et al. 2017 (2).

L.4.3 HRQoL (EQ-5D-5L)

The pattern of missing data and completion from the EQ-5D-5L index score (Denmark value set) over time is demonstrated in Table 119 for the Q-F ITT population.

Table 119 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Induction Phase Cycle 1 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Induction Phase Cycle 2 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 1 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 1 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 2 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 2 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 3 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 3 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 4 Day 6	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 4 Day 28	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 1 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 4 Day 1	[redacted]	[redacted]	[redacted]	[redacted]

Consolidation Phase Cycle 7 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 10 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 22 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 31 Day 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation Phase Cycle 34 Day 1	[redacted]	[redacted]	[redacted]	[redacted]

Source: Daiichi Sankyo 2023 (6).

EQ-5D-5L results

An MMRM analysis was performed adjusting for score at baseline, treatment, time, and a treatment-by-time interaction. It shows the change from PRO baseline effect of quizartinib vs. placebo on the EQ-5D-5L index score (DK value set) over time. The results demonstrate an improvement in EQ-5D-5L index score (DK value set) over time in both treatment arms compared to PRO baseline results. This data is presented in Table 120. Figure 56 displays the mean change (including error bars showing the standard deviations) from baseline for both quizartinib and placebo.

Figure 56 EQ-5D-5L DK index score - Least Square Means estimate by treatment across time. PRO, ITT Analysis Set.

Notes: Least Square Means and associated Confidence Interval from Mixed Model Repeated Measures: Changes in the QoL scores = Baseline + Treatment + Time + Treatment x Time with a AR (1) structure of covariance matrix for residuals.
Source: Daiichi Sankyo 2023 (8)

Table 120 HRQoL EQ-5D-5L summary statistics (ITT population)

	Quizartinib (N 254) Mean [95% CI)	Placebo (N=255) Mean [95% CI)	Quizartinib vs. placebo [95% CI)
	Mean, [95% CI][a]	Mean, [95% CI][a]	Difference (95% CI) [a]
Induction Cycle 1 Day 28	[redacted]	[redacted]	[redacted]
Induction 2LCycle 2 Day 28	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 1 Day 6	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 1 Day 28	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 2 Day 6	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 2 Day 28	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 3 Day 6	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 3 Day 28	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 4 Day 6	[redacted]	[redacted]	[redacted]
Consolidation 2LCycle 4 Day 28	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 1 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 4 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 7 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 10 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 13 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 16 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 19 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 22 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 25 Day 1	[redacted]	[redacted]	[redacted]

Maintenance 2LCycle 28 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 31 Day 1	[redacted]	[redacted]	[redacted]
Maintenance 2LCycle 34 Day 1	[redacted]	[redacted]	[redacted]

Notes: a = Least Square Means and associated Confidence Interval from Mixed Model Repeated Measure
Source: Daiichi Sankyo 2023 (8)

HSUVs used in the health economic model

The value used in the economic model for the Naïve scenario are shown in Table 121.

Table 121 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff used	Comments
Health state utilities				
Induction	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
First remission consolidation	[redacted]			Estimate is based on mean of both trial arms.
First remission continuation and First CR	[redacted]			Estimate is based on mean of both trial arms.
Relapse after first remission	[redacted]			Estimate is based on mean of both trial arms.
Refractory	[redacted]			Estimate is based on mean of both trial arms.
Second CR	[redacted]			90% of the valued for First CR
Relapse 2	[redacted]			90% of the Relapse 1L value
HSCT treatment 1L	0.613 [0.362, 0.835]	EQ-5D	Not speci-fied	Estimates were derived from NICE TA 523
HSCT recovery 1L	0.810 [0.405, 0.995]			
HSCT maintenance 1L	0.826 [0.401, 0.998]			
HSCT treatment 2L	0.552 [0.333, 0.760]			90% of the 1L health state. KOL opinion
HSCT recovery 2L	0.729 [0.403, 0.952]			90% of the 1L health state. KOL opinion
HSCT maintenance 2L	0.743 [0.406, 0.963]			90% of the 1L health state. KOL opinion
Disutility				

GVHD	0.173 [0.111, 0.2456] *	Values used in NICE TA 523

Notes: Calculated based on a standard error of 0.03

Source: Daiichi Sankyo 2023 (8); Midostaurin NICE TA 523).

Appendix M. Additional endpoints from Q-F and RATIFY

M.1 Event free survival in QuANTUM First

Table 123 presents the results of the EFS endpoints. The analysis of EFS per IRC assessment was based on lack of induction treatment success (i.e., not having CR) during a 42-day period from the start of the last induction cycle (as defined in the United States (US) Food and Drug Administration (FDA) AML guidance) in alignment with the European public assessment report (126, 127). The median EFS was 0.0 (0.0, 7.6) months in the quizartinib arm and 0.5 (0.0, 5.1) months in the placebo arm. There was no statistically significant difference between the two arms. Because the analysis of EFS was not statistically significant, formal hierarchical testing was not continued.

Table 122 Event free survival (with a 42-day window) (Q-F < 60)

Estimate	Quizartinib (n=161)	Placebo (n=162)
Subjects (%) with events	[redacted]	[redacted]
Median EFS months (95% CI)	0.0 (0.0, 7.6)	0.5 (0.0, 5.1)
HR (relative to placebo), 95% CI	0.859 (0.662, 1.115)	
p-value	[redacted]	

Table 123 Event free survival rates

EFS rate	Quizartinib (n=161)	Placebo (n=162)
6 months EFS rate, % (95% CI)	[redacted]	[redacted]
12 months EFS rate, % (95% CI)	[redacted]	[redacted]
18 months EFS rate, % (95% CI)	[redacted]	[redacted]
24 months EFS rate, % (95% CI)	[redacted]	[redacted]
30 months EFS rate, % (95% CI)	[redacted]	[redacted]
36 months EFS rate, % (95% CI)	[redacted]	[redacted]

Source: Daiichi Sankyo Inc., 2024, table 4.4.2b (63).

The EFS curves are shown in Figure 57 indicating a minor separation between the quizartinib arm and the placebo arm favouring quizartinib. Half of the patients experience an event at start of follow-up due to the stringent definition of induction treatment failure

using the 42-day window with event date assigned to Day 1 (i.e., many subjects with true refractory disease and those with CR achieved after Day 42 of their last induction chemotherapy were considered to have EFS events on Day 1). An extended period for assessing CR may have allowed patients to recover from quizartinib myelosuppressive effects. If patients were impacted by myelosuppression in the induction phase, without time to manage it appropriately, it would not have been possible to differentiate patients experiencing the AE from patients with induction treatment failure given the method of measurement used for CR.

Figure 57 KM of event-free survival (with a 42-day window) (Q-F < 60)

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Source: Daiichi Sankyo Inc., 2024, Figure 4.4.2b.

M.2 Duration of Complete Remission in QuANTUM First

Median duration of complete remission (DUR) was included in Q-F as an exploratory endpoint. Median DUR was NE for quizartinib and 16.5 (9.4, NE) months for placebo (Table 21). Figure 58 suggest a continued separation of the curves after the first 3 months of follow-up.

Table 124. Analysis of DUR (Q-F < 60)

Statistics	Quizartinib (N=90)	Placebo (N=90)
Subjects with an event, n (%)		
Median DUR (months) (95% CI)	NE (NE, NE)	16.5 (9.4, NE)
Hazard ratio (95% CI)	0.432 (0.267, 0.699)	
p-value		
DUR rate, % (95% CI)		
6 months		
12 months		

24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]

Sources: Daiichi Sankyo Inc, 2024, table 4.4.2g (63)

Figure 58. KM plot for DUR in patients who achieved CR during induction (Q-F<60)

Abbreviations: CI = confidence interval; CR = complete remission; KM = Kaplan-Meier; NE = not estimable; Q-F=Quantum-First. Sources: Daiichi Sankyo Inc, 2024, figure 4.4.2g (63)

M.3 Event Free Survival in RATIFY

For the analysis of EFS, 536 events were observed: 298 failures to achieve protocol-specified CR, 181 relapses, and 57 deaths without relapse. Median EFS was 8.2 months (95% CI 5.4, 10.7) in the midostaurin group and 3.0 months (95% CI 1.9, 5.9) in the placebo group (*P* = 0.002). Patients assigned to the midostaurin group had a 21.6% lower likelihood of having an event than patients assigned to the placebo group (HR = 0.78; 95% CI 0.66, 0.93; *P* = 0.002), with 4-year EFS rates of 28.2% in the midostaurin group and 20.6% in the placebo group (Table 125). Figure 59 shows KM curves for EFS. There is a clear separation between the midostaurin arm and the placebo arm favouring midostaurin.

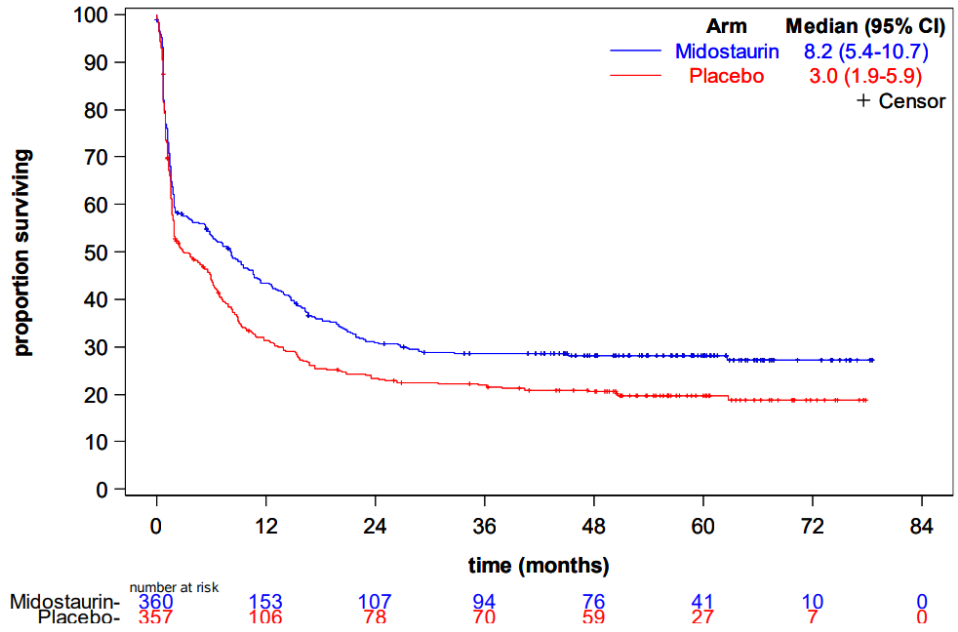

Figure 59. Kaplan-Meier plot of event-free survival (RAIFY ITT population)

Abbreviations: CI = confidence interval; ITT = intention-to-treat.
Source: Stone et al., 2017, appendix (2).

The benefit of midostaurin with respect to EFS survival was consistent across the *FLT3* subtypes (Figure 60).

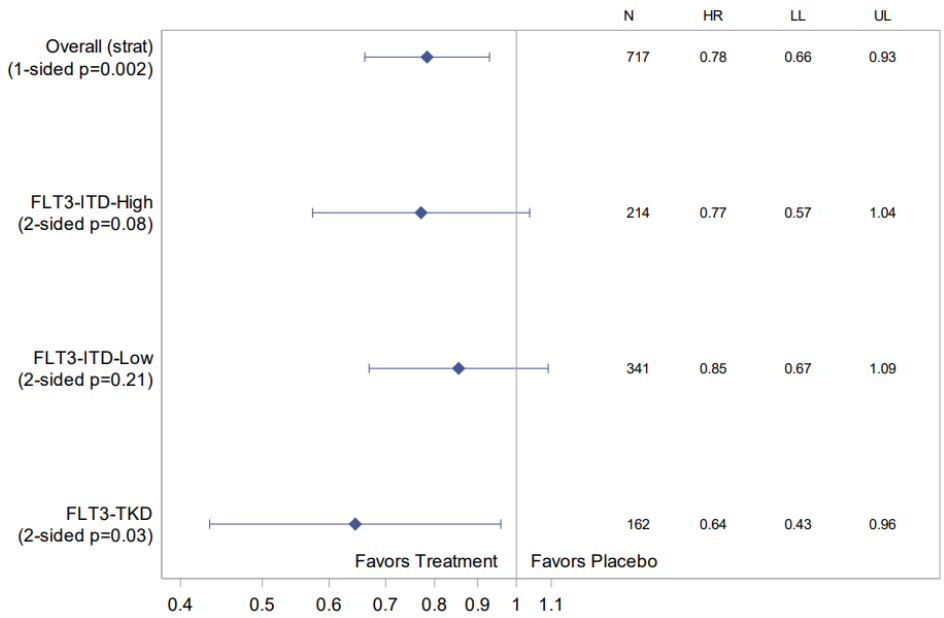

Figure 60. Forest Plot of EFS HR by *FLT3* subgroup (ITT population)

Abbreviations: *FLT3* = FMS-like tyrosine kinase 3 mutation; ITD = internal tandem duplication;; LL = lower limit (of the 95% confidence interval); TKD = tyrosine kinase domain; strat = stratified; UL = upper limit (of the 95% confidence interval).
Notes: *P* value from the Score set. Overall *P* value stratified on *FLT3* subtype and gender. Source: Stone et al., 2017, appendix (2)

Table 125. Summary of EFS outcomes in RATIFY (ITT population)

Estimate	Midostaurin (N = 360)	Placebo (N = 357)	Analysis (midostaurin vs. placebo)
Median EFS months (95% CI)	8.2 (5.4, 10.7)	3.0 (1.9, 5.9)	*P* = 0.002*
HR (95% CI), *P* value	N/A	N/A	0.78 (0.66, 0.93), *P* =0.002**
4-year EFS rate, %	28.2	20.6	N/A

Notes: * log-rank p-value, stratified on FLT3 subtype. ** Score test p-value, stratified on FLT3 subtype. Source: Stone et al., 2017 (2).

Figure 61 shows KM curves for EFS. There is a clear separation between the midostaurin arm and the placebo arm favouring midostaurin.

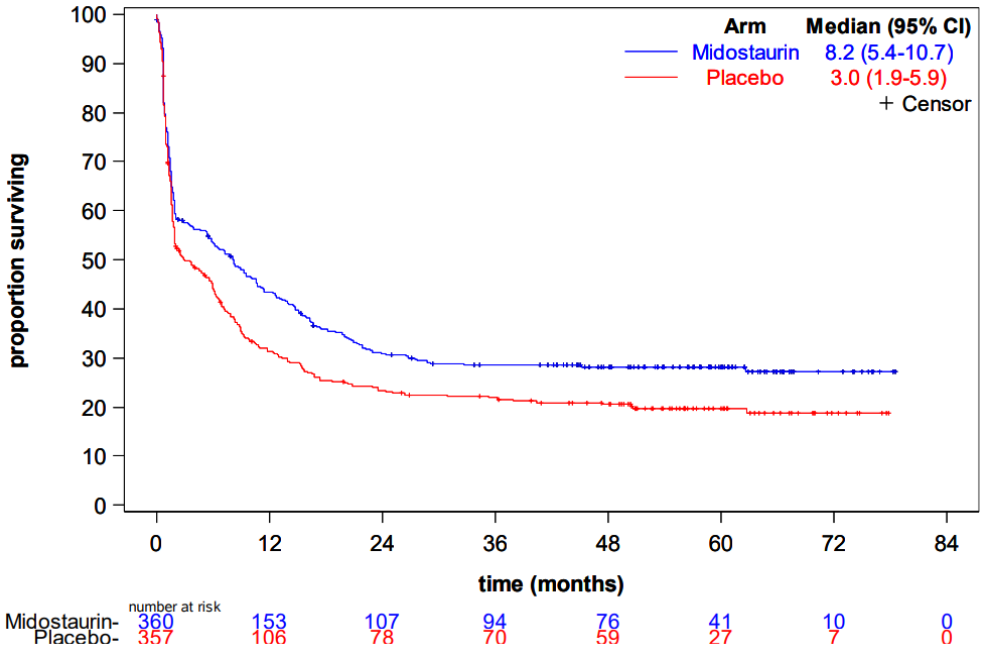

Figure 61. Kaplan-Meier plot of event-free survival (RAIFY ITT population)
Source: Stone et al., 2017, appendix (2).

The benefit of midostaurin with respect to EFS survival was consistent across the *FLT3* subtypes (Figure 62).

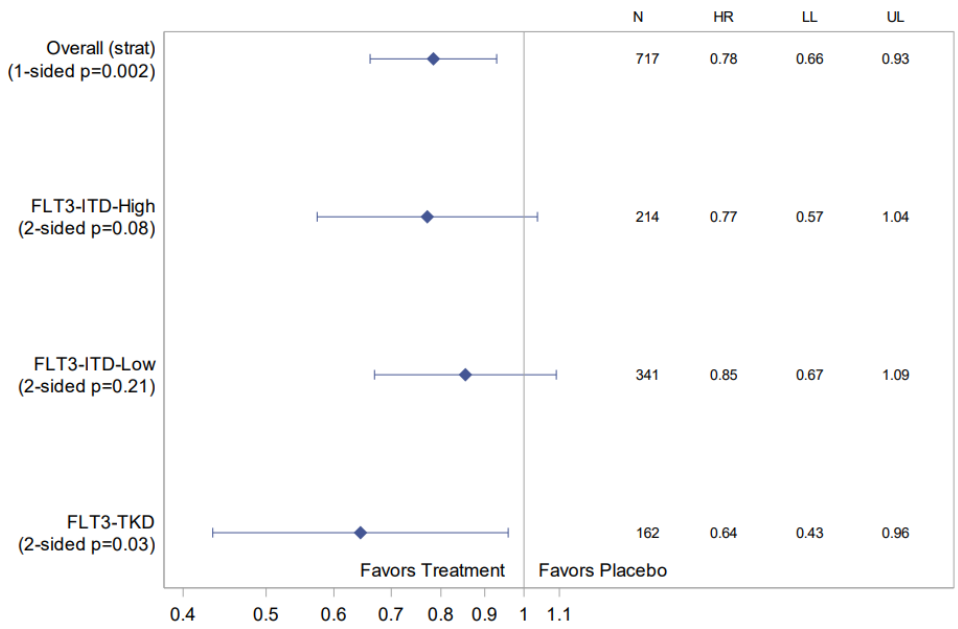

Figure 62. Forest Plot of EFS HR by *FLT3* subgroup (ITT population)

Abbreviations: *FLT3* = FMS-like tyrosine kinase 3 mutation; HR = hazard ratio; ITD = internal tandem duplication; ITT = intention-to-treat; LL = lower limit (of the 95% confidence interval); TKD = tyrosine kinase domain; strat = stratified; UL = upper limit (of the 95% confidence interval).
Notes: *P* value from the Score set. Overall *P* value stratified on *FLT3* subtype and gender.
Source: Stone et al., 2017, appendix (2)

Appendix N. Additional description of transition probability assumptions

N.1 Transitions from *Induction* health state

For the quizartinib arm, TPs from the *Induction* health state were derived from Q-F trial data. Patients in the *Induction* state can transition to *CR1*, *Refractory*, *Death* or remain in the *Induction* state for a second cycle of induction treatment (maximum of 2 cycles).

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

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

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

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

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

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

Transitions were calculated based on the number of patients in induction at the start of each round. The weighted number of patients used to calculate the TPs are presented in Table 126

Table 126. Number of patients transitioning out of Induction, per induction cycle based on the adjusted Q-F population

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

Source: Daiichi Sankyo, 2022 (8)

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

In the RATIFY study, by design and protocol, only results based on CR were reported; CRi was not collected as at the time of the study and the concept of haematological recovery was not established. Consequently, the MAIC was restricted to comparing the rates of CR (rather than CRc).,

As presented in section 7, the MAIC of CR between quizartinib and midostaurin based on the adjusted QuANTUM-First population and RATIFY FLT3-ITD populations showed numerically unfavourable but not statistically significantly different outcomes with quizartinib as compared to midostaurin (OR: 0.92; 95% CI: 0.42 to 1.97) (7). For the midostaurin regimen, TPs of induction to first CR (1st and 2nd rounds of induction) were derived by combining

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

N.2 Transitions from *Complete Remission* (*CR1)* health state

TPs from *CR1* to *Relapse1* and *Death* are time-variant and were derived from relapse after CRc and survival after CRc data from adjusted Q-F (quizartinib) population and the MAIC analysis (midostaurin). The survival curves informing these TPs are presented in section 8.1.1 and Appendix D

Due to the lack of data and discrepancies in the definition of remission in the Q-F and RATIFY trials, the HSCT rate could not be included as an endpoint in the MAIC. Therefore, the proportion of patients receiving HSCT was modelled as a function of complete response. This assumes that a fixed proportion of patients who achieve complete remission will proceed to protocol-specified HSCT.

Table 127. Analysis of protocol-specified HSCT rate in QuANTUM-First

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

Notes: a. Subjects with protocol-specified HSCT are subjects who underwent HSCT directly following protocol treatment with no intervening AML therapy (excluding conditioning regimens).

The transition from *CR1* to *HSCT 1L* for quizartinib was based on the proportion of patients receiving protocol-specified HSCT after achieving CRc, as per the QuANTUM-First ITT analysis set (Table 127). For midostaurin the transition was based on Stone et al. (2). Therefore, the modelled transplant rate for each treatment is only dependent on the proportion of patients in the CR1 health state at the time of HSCT.

Table 128. Transition probabilities from CR1

Transition from:	Transition to:	Quizartinib		Midostaurin	
		Inputs	Reference	Inputs	Reference
CR1	CR1	Residual	Residual	Residual	Residual
	R1	Relapse from CRc curve from adjusted QuANTUM-	QuANTUM-First trial data. Refer to	Combing HR from MAIC with the	MAIC analysis (**Error! Reference**

	First (CRc cohort of ITT)	section D.1 for more details	reference treatment (i.e. quizartinib)	**source not found.**)
HSCT 1L (per cycle for 4 – cycles)	[redacted]	TP is calculated by use of Excel "Solver" function. The function is used to set the TP so that the share of patients who move to HSCT tunnel states equal the fraction of patients who underwent HSCT in Q-F. [redacted] patients with protocol-specified HSCT after CRc out of 268 patients in the ITT analysis set in quizartinib arm	[redacted]	midostaurin: Similar approach to quizartinib, using the "Solver function"In Stone et al., 2017. Transplantation was performed during the first complete remission in 28.1% of the patients in the midostaurin
Dead (time-varying)	Death from CRc curve from adjusted QuANTUM-First (censored for HSCT)	QuANTUM-First trial data. Refer to section D.1for more details	Combing HR from MAIC with the reference treatment (i.e. quizartinib)	MAIC analysis

N.3 Transitions from *Post-allo-HSCT maintenance* to *Post-allo-HSCT relapse (1L and 2L)*

Very few patients who received protocol-specified HSCT after achieving CRc subsequently relapsed (n=[redacted] in the quizartinib arm and n=[redacted] in the placebo arm) in the QuANTUM-First ITT analysis set. Due to this immaturity of the data, the time-varying survival for post-HSCT 1L relapse was too uncertain to be informative. Therefore, time-invariant inputs sourced from the adjusted QuANTUM-First population were used for quizartinib in the model to inform the transition from HSCT 1L to post-HSCT 1L relapse. For midostaurin in 1L it was assumed that the treatment effect would be the same as for the placebo-arm in Q-F, since midostaurin maintenance is not licensed or recommended post-HSCT. Same TPs were used in 2L for quizartinib and midostaurin.

Table 129. Transition probabilities from HSCT to post HSCT relapse, 1L and 2L, by treatment arm

Transition from:	Transition to:	Quizartinib regimen		Midostaurin regimen	
		Inputs	Reference	Inputs	Reference

Allo-HSCT 1L	1L post-HSCT relapse	[redacted]	QuANTUM-First trial data, quizartinib arm. Assuming time-invariant transitions, [redacted] of [redacted] patients who had HSCT relapsed over an average length of [redacted] days	[redacted]	Assumed equal to QuANTUM-First trial data, placebo arm. Assuming time-invariant transitions, [redacted] of [redacted] relapsed over an average length of [redacted] days
2L post-HSCT maintenance	2L post-HSCT relapse (Relapse 2)	[redacted]	Assumed 50% higher than 1L for the placebo arm of Q-F based on clinical expert opinion	[redacted]	Assumed 50% higher than 1L for the placebo arm of Q-F based on clinical expert opinion

Source: Daiichi Sankyo, Inc., 2022 (8);

N.4 Transitions from 1L and 2L HSCT to Death

The same transition probabilities were used for quizartinib and midostaurin to inform mortality in post HSCT maintenance 1L and 2L. Within the 13 tunnel states for *HSCT 2L*, comprising one year, only transitions to *Death* were allowed in the model, relapse was not permitted (as a simplifying assumption).

Data to inform the TPs for the *HSCT 1L* and *HSCT 2L* tunnel states were derived from Styczynski et al, 2019 (59) with the transitions detailed in Table 130. Styczynski et al. 2019 is a retrospective, observational retrospective observational study analysed post-HSCT outcomes in AML, ALL, and CML patients reported by 588 centres across 51 countries, including Denmark, using the EBMT database data from 1980 to 2015. Isolated Danish specific data was not identified. The economic analysis focused on Cohort 2, comprising 71,494 patients who underwent transplantation between 2002 and 2015, with a median age of 41. AML patients constituted 63.5% of this cohort (45,386 patients). Over 90% of Cohort 2 underwent allogeneic HSCT (64,661) with less than 10% receiving autologous transplants. Over 90% of Cohort 2 was at their first transplantation. The study did not specify the geographic origin of the included patients. The source was deemed appropriate as Denmark is part of the EBMT database.

Table 130. HSCT 1L & 2L transition probability of disease related death, per cycle

Transition from	**Transition probability, %**	**Reference**

HSCT 1L & 2L, tunnel state 1	3.7	Styczynski et al, 2019 Cohort 2, Figure 1a 2,797 deaths out of 7,1494 patients over 30 days
HSCT 1L & 2L, tunnel states 2-3	4.3	Styczynski et al, 2019 Cohort 2, Figure 1b 6,403 deaths out of 61,220 patients over 70 (100-30) days
HSCT 1L & 2L recovery, tunnel states 1-10	2.7	Styczynski et al, 2019 Cohort 2, Figure 1c 13,449 deaths out of 58,609 patients, over 265 (365-100) days
Post-HSCT 1L & 2L recovery	0.4	Styczynski et al, 2019 Cohort 2, Figure 1d 7,527 deaths out of 37,487 patients, over four years (1,460 days)

N.5 Transitions from *Refractory* and *CR2*

As mentioned in section 8.3.1 transitions from relapse data for subsequent treatment is not available in either the QuANTUM-First or RATIFY trials. Therefore, the data to inform the TPs from the *Refractory* and *CR2* health states were derived from pooled data from the ADMIRAL trial (57). Transition probabilities were assumed constant across 2L treatments for both the quizartinib and midostaurin arm, supported by ADMIRAL subgroup analyses showing similar death hazard ratios for patients with or without prior FLT3i treatment. A comparison of key patient characteristics between Q-F and ADMIRAL can be found in Table 131

The ADMIRAL trial, being the Phase 3 study comparing gilteritinib to salvage chemotherapy in relapsed or refractory FLT3-mutated AML, was the primary source of efficacy data for this indication (57). Transition probabilities were derived from pooled ADMIRAL data, as the model included gilteritinib and FLAG-Ida as 2L regimens. While patient characteristics in ADMIRAL were broadly similar to the Q-F population, ADMIRAL included both FLT3-ITD+ and TKD+ patients, while Q-F patients were younger and exclusively FLT3-ITD+. ADMIRAL's primary endpoints were OS, CR, and CR with partial haematological recovery, and its results are likely applicable to the Danish population.

Table 131. Comparison of key patient's characteristics in ADMIRAL and Q-F

	ADMIRAL (N=371)	SORMAIN (N=83)	Q-F ITT (N=539)	Q-F adjusted ≤ 60 y.o. ¥ ([redacted])
Age (Median)	62	54	56	49
Sex (female)	201 (54%)	42 (51%)	294 (55%)	[redacted]
Cytogenetic risk status*				
Favorable	5 (1%)	0 (0%)	33 (6%)	N/C
Intermediate	271 (73%)	76 (92%)	390 (72%)	N/C
Unfavorable	37 (10%)	4 (5%)	46 (9%)	N/C
Unknown	58 (16%)	3 (4%)	69 (13%)	N/C
FLT3 mutation subtype				
ITD only	328 (88%)	83(100%)	539 (100%)	[redacted] (100%)
TKD	31 (8%)	NR-	-	-
ITD and TKD	7 (2%)	NR	-	-

* 1 patient with missing cytogenetic risk status in Q-F.

[¥]In the MAIC, the Q-F population was matched to the RATIFY FLT3-ITD+ subpopulation. * 1 patient with missing cytogenetic risk status in Q-F. In SORMAIN, cytogenetic risk defined as low, intermediate and high
Source: Perl (2019) (57)

In 2L management of AML, although not as common, HSCT plays an important role in treatment goals (128). HSCT is the only curative therapy for patients with primary refractory disease and offers the best chance for cure in those who relapse after initial chemotherapy (129). As a result, patients refractory to 1L treatment but achieving complete remission with gilteritinib are eligible for transplant. However, patients who received HSCT in 1L treatment were not able to receive HSCT in 2L in the model. This was in line with clinical expert opinion which advised that a negligible proportion of patients would receive a second HSCT(130).

N.6 Conversion of time-to-event data into time-dependent transition probabilities

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

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

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

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

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

with λ being the scale parameter and γ being the shape parameter of the distribution. These are estimated from the regression analysis conducted in R when fitting the Weibull distribution. Substituting and rearranging the cumulative hazard function in Equation 1 into the general form in Equation 2, results in Equation 3, which can be used to estimate time-dependent TPs.

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