Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukemia

EUnetHTA report

eunethta

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No.74

EUnetHTA Joint Action 3 WP4

Rapid assessment of pharmaceutical technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment

MIDOSTAURIN WITH STANDARD CHEMOTHERAPY

IN FLT3-POSITIVE ACUTE MYELOID LEUKAEMIA

Project ID: PTJA01

Version 1.3, 6th November 2017

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	**11/09/2017**	First draft.
V1.1	**09/10/2017**	Input from dedicated reviewers has been processed.
V1.2	**17/10/2017**	Input from medical editor has been processed.
V1.3	**06/11/2017**	Input from external experts and manufacturer(s) has been processed.

Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

EUnetHTA Joint Action 3 is supported by a grant from the European Commission. The sole responsibility for the content of this document lies with the authors and neither the European Commission nor EUnetHTA are responsible for any use that might be made of the information contained therein.

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A single Romanian patient with acute myeloid leukaemia (AML) was consulted during the scoping phase to gain insight into patient perspectives related to AML treatment.

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Conflict of interest

All authors and dedicated reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form. One external expert, Dr. Baron, has declared a financial or another relationship with the Developing and/or Producing and/or Distributing Organisation (DPDO) for the technology or comparators undergoing assessment, and thus has a conflict of interest according to the EUnetHTA guidelines for handling conflict of interest. Dr. Baron received reimbursement for accommodation, travel costs and congress fees for participation to an international haematology meeting in the last 5 years from Novartis through his institution. Dr. Baron has no other conflicts of interest related to the topic of midostaurin or to Novartis to declare. According to the EUnetHTA guidelines for handling conflict of interest, the involvement of Dr. Baron as external expert is acceptable for commenting on the draft project plan and draft assessment without having access to any potentially confidential material.

How to cite this assessment

Please, cite this assessment as follows:

Finnish Medicines Agency, Norwegian Medicines Agency. Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukaemia. Rapid assessment of other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. EUnetHTA Project ID: PTJA01. 2017.

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LIST OF ABBREVIATIONS

ADE	daunorubicin, cytarabine, etoposide
AE	adverse event
AlloSCT	allogeneic stem cell transplant
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukaemia
ASH	American Society of Hematology
BID	twice daily
BSA	body surface area
BSC	best supportive care
C	cytarabine
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIR	cumulative incidence of relapse
CN AML	cytogenetically normal acute myeloid leukaemia
CR	complete remission
CREN	crenolanib
CSF	cerebrospinal fluid
CSR	clinical study report
Cy	cyclophosphamide
CYP	cytochrome P450
D	daunorubicin

DFS	disease-free survival
DOICU	Declaration of interest and confidentiality undertaking
E	etoposide
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	event-free survival
EHA	European Hematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
Ev	everolimus
FAS	full analysis set
FDA	US Food and Drug Administration
FLAG-IDA	fludarabine + cytarabine + idarubicin
FLT3	FMS-like tyrosine kinase 3
FLT3i	FLT3 inhibitor
G-BA	Gemeinsame Bundesausschuss (Federal Joint Committee)
G-CSF	granulocyte-colony stimulating factor
GILT	gilteritinib
GO	gemtuzumab ozogamicin
HAS	Haute Autorité de Santé (National Authority for Health)

HDAC	high-dose cytarabine
HDCT	high-dose chemotherapy
HGF	haematopoietic growth factors
HLA	human leukocyte antigen
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
I	idarubicin
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IDAC	intermediate-dose cytarabine
IM	intramuscular
ITD	internal tandem duplications
IV	intravenous
L	lenograstim (granulocyte-colony stimulating factor)
LDAC	low-dose cytarabine
LEST	lestaurtinib
LVEF	left ventricular ejection fraction
M	mitoxantrone
MAA	marketing authorisation application
MACE	amsacrine, cytarabine, and etoposide
MAH	marketing-authorisation holder
MDS	myelodysplastic syndrome

MEC	mitoxantrone + etoposide + cytarabine
MeSH	Medical Subject Headings
MidAC	mitoxantrone and cytarabine
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trial
NE	not estimable
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NOS	not otherwise specified
NPM1	nucleophosmin 1
NR	not reported
OS	overall survival
P	placebo
PAES	postauthorisation efficacy study
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-analyses – Protocol
PS	performance status
QUIZ	quizartinib
RCT	Randomised Controlled Trial
REA	Relative Effectiveness Assessment
RFS	relapse-free survival

RR	relative risk
S	sorafenib
SAE	serious adverse event
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SC	subcutaneous
SCT	stem cell transplant
SD	standard deviation
SmPC	Summary of Product Characteristics
SoC	standard of care
TKD	tyrosine kinase domain
UK	United Kingdom
US	United States
WBC	white blood cell
WHO	World Health Organization

SUMMARY OF THE RELATIVE EFFECTIVENESS OF MIDOSTAURIN

Scope

The scope can be found here: Scope

Introduction

This is the assessment of the relative effectiveness of midostaurin in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy for patients in complete response, followed by midostaurin monotherapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are *FLT3* mutation positive. Relevant alternative therapies had been established based on European guidelines and recommendations.

Methods

The objective in the clinical effectiveness and safety domains of this assessment was to identify studies related to the beneficial and harmful effects of midostaurin and its relevant comparators for the treatment of adult patients with newly diagnosed AML who are fit for intensive chemotherapy. The manufacturer provided a systematic literature review of the evidence, which was critically assessed by authors of this assessment.

The following electronic databases were included in the marketing-authorisation holder (MAH) literature search: Embase, via the Embase.com platform; the Cochrane Library database Central Register of Controlled Trials; Medline and Medline InProcess and electronic publications ahead of print via PubMed; and clinicaltrials.gov, WHO (International Clinical Trials Registry Platform metaregistry) and European (EU Clinical Trials Register) registries. Hand-searches included conference proceedings for the American Society of Hematology 2016 and European Hematology Association 2016/17 (searched for abstracts and e-posters) and reference lists of included publications. The final search of databases was performed on 7th June 2017 and final congress searches were performed on 26th June 2017. The search protocol was included as part of the submission.

Overall, the authors considered that the reporting of the search followed the requirements of the EUnetHTA guidelines and reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) statement. The search was conducted approximately 2 months before the start of the assessment, and was considered to be up to date.

In total, three studies (RATIFY, IIT (AMLSG 16-10 / CPKC412DE02T) and UK NCRI AML17 trials) were included in the assessment. Risk of bias assessment was conducted at both the study and outcome level for RCTs by the authors of this assessment. GRADE was used to assess the quality of evidence by authors.

Data and results for RATIFY and IIT studies were included in the MAH submission file. According to MAH, these data were presented in the submission file as in the CSR. Results for the UK NCRI AML17 trial were extracted from the publications by the authors. Direct comparisons were represented as in the MAH submission file. Indirect comparison of midostaurin with standard induction ("7+3 regimen) and consolidation therapy versus induction ("10+3 regimen) and consolidation chemotherapy with high-dose daunorubicin (90 mg/m^2/day) during induction was performed by the authors using the Bucher method according to the EUnetHTA guideline. In the AML17 randomisation scheme, FLT3 patients had a second course with daunorubicin 50 mg/m2/day plus cytarabine +/- lestaurtinib and one or two further courses of high dose cytarabine.

Results

Description of technology and comparators

Midostaurin is a new orally administrated multi-target receptor tyrosine kinase inhibitor [B0001]. It was designated as an orphan medicinal product on 29th July 2004. Midostaurin received a positive CHMP opinion from the European Medicines Agency (EMA) on 20th July 2017. Marketing authorisation (EC decision) was granted for midostaurin on 18th September 2017 for the following indication: in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single-agent maintenance therapy, for adults with newly diagnosed AML who are FLT3 mutation positive. Midostaurin gained regulatory approval from the US Food and Drug Administration (FDA) on 28th April 2017 and from Swissmedic on 4th May 2017 followed by Health Canada approval on 21st July 2017 and EU approval (EC decision) on 18th September 2017. While the FDA and Health Canada approvals were restricted to the induction and consolidation phase, the EMA and Swissmedic approvals included induction, consolidation and the maintenance phases [A0020].

The marketing authorisation application (MAA) for midostaurin included a second indication as monotherapy for the treatment of adults with aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm, or mast cell leukaemia. This indication is not relevant for this relative efficacy assessment and is not considered in the report. [A0020]

Midostaurin will be available as 25-mg soft capsules. The recommended dose of midostaurin in AML is 50 mg twice daily on days 8–21 of each cycle of induction and consolidation chemotherapy, followed by 50 mg daily as a single agent for up to 12 months.

Currently, there are several treatments recommended for AML, but none is specific for FLT3 mutation-positive AML. The following treatments were considered the most-relevant comparators: standard induction and consolidation chemotherapy (cytarabine in combination with daunorubicin 60 mg/m^2/day during the induction phase) and induction and consolidation chemotherapy with daunorubicin 90 mg/m^2/day during the induction phase, as recommended by the Norwegian guidelines (Appendix 1,Table A8) [B0001].

Health problem

The health condition relevant for the present assessment is newly diagnosed FLT3 mutation-positive AML. AML is a haematological malignancy characterised by abnormal growth of haematopoietic cells of myeloid lineage in the bone marrow, blood and other tissues. Overall, the 5-year survival rate for AML is 20%–30%. Younger patients have better outcomes compared with older patients. Patients with FLT3 mutation-positive AML have worse outcomes for overall survival (OS), time to relapse and disease-free survival (DFS) compared with patients without FLT3 mutation-positive disease. [A0007]

AML is a rare condition, with an estimated incidence of 3.7 per 100,000 for the EU overall, and is mainly diagnosed in older patients. Approximately one-third of patients have FLT3 mutation-positive disease. [A0023].

Clinical effectiveness

Available evidence

The assessment of clinical effectiveness was based on three studies: RATIFY trial, IIT-trial and UK NCRI AML17 trial.

RATIFY was a randomised phase III study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo in treatment-naive patients with FLT3-mutated AML. In total, 717 patients aged 18–60 years were included in the full analysis set of the trial. This was the most important study to this assessment and is the pivotal trial of midostaurin this indication.

Investigator-initiated trial (IIT trial, AMLSG 16-10 / CPKC412DE02T) is a single-arm phase II trial involving 145 patients (aged 18–70 years) receiving midostaurin with standard induction and consolidation therapy. This study provided supporting data especially on older patients (over 60-years old). These data were mainly used to characterise the treatment outcomes in an older population.

The UK NCRI AML17 trial compared standard chemotherapy with daunorubicin 60 mg/m^2 to high-dose daunorubicin. The trial was terminated prematurely due to a significantly higher 60-day mortality rate observed in the 90 mg/m^2 vs 60 mg/m^2 daunorubicin group in the overall study population, not restricted to patients with FLT3 mutation. However, there was a significant interaction in the effect by FLT3 mutation. The results of the post-hoc exploratory subgroup analysis considering FLT3 positive patients (n=200, median follow-up of 28 months) of this study were applied only to the indirect comparisons related to OS.

Overall survival [D0001]

In the RATIFY trial, the risk of death was reduced by 23% during the follow-up for the midostaurin versus placebo groups (HR 0.77 [95% CI 0.63–0.95]; p=0.0078). The proportion of patients alive in the midostaurin and placebo treatment arms were:

- 1 year – 76% (95% CI: 0.72–0.81) versus 68% (95% CI: 0.62–0.72)
- 5 years – 51% (95% CI: 0.45–0.56) versus 43% (95% CI: 0.38–0.49)

Similar to the OS results, results for OS censored at SCT showed a reduced risk of death for patients treated with midostaurin over placebo (HR 0.75 [95% CI: 0.54–1.03]; p=0.0373).

In the single-arm IIT trial, the proportion of younger patients (≤60 years) alive was 53.7% at the 2-year follow up. The proportion of older patients (>60 years) was 45.2%. The median survival was 28.5 months and 15.5 months, respectively.

A difference in OS effect was observed for men versus women in a prespecified subgroup analysis (HR=0.53 [95% CI: 0.39–0.72] for men and HR=1.01 [95% CI: 0.76–1.34] for women). This heterogeneity was not observed in other efficacy endpoints. No other relevant heterogeneity in the OS effect was observed in the subgroup analyses, including SCT status (undergoing SCT or not undergoing SCT) and NPM1 status (mutated or wild type).

Indirect results comparing daunorubicin 90 mg/m^2 in the first induction cycle ("10 + 3" regimen) followed by a second course and consolidation versus midostaurin plus standard induction ("7 + 3" regimen) and consolidation, showed no difference between the treatments in terms of OS (HR=0.84 [95% CI: 0.54–1.31]). However, several serious limitations apply to this indirect comparison.

Disease progression, treatment response and relapse rate [D0006]

Event-free survival (EFS) was improved by 27% compared with standard induction and consolidation chemotherapy (HR=0.73, 95% CI: 0.61–0.87, p=0.0001). EFS results censored at SCT were consistent with this result (HR=0.76, 95% CI: 0.63–0.92, p=0.0019). The effect of midostaurin on EFS was homogeneous across the subgroups. In the IIT trial, median EFS was 13.8 months in patients aged ≤60 years and 9.3 months in patients over 60 years of age.

Disease-free survival (DFS) from first complete remission (CR) was improved by 34% compared with standard induction and consolidation chemotherapy (HR= 0.66, 95% CI: 0.52–0.85, p=0.0006) and DFS censored at SCT improved by 28% compared with standard induction and consolidation chemotherapy (HR=0.72, 95% CI: 0.54–0.97, p=0.0150).

Overall, the CR rate was higher in the midostaurin group than in standard induction and consolidation chemotherapy (65% versus 58%, p=0.027, one sided). In the IIT trial, a slightly higher proportion of patients in CR was observed in patients ≤60 years of age than in patients over 60 years of age (77% vs. 67%).

Comparison of the cumulative incidence of relapse (CIR) between the two treatment groups showed that midostaurin reduced the risk of relapse compared with standard induction and consolidation chemotherapy (HR 0.676 [95% CI: 0.52–0.89]; p=0.0023). Censoring for SCT reduced the difference between the treatment groups (HR 0.761 (0.561–1.031); p=0.0387).

Generic and disease-specific quality of life [D0012, D0013]

There were no results available on the effect of midostaurin on the generic health-related quality of life or disease-specific quality of life. Quality-of-life aspects have not been investigated in the studies completed to date.

Safety

All patients in the RATIFY trial experienced at least one adverse effect (AE) of any grade regardless of relation with the study drug. All patients in the placebo group and all except one patient in the midostaurin group experienced grade 3–4 AEs. Approximately 50% of the patients in both groups experienced a serious AE (SAE) and approximately 75% of patients in both groups reported at least one grade 3–4 AE considered to be related to treatment. Most AEs were reported during the induction and consolidation phases and were less frequently reported during the continuation phase. There were 36 deaths-on-treatment (i.e., within 30 days of the last treatment; 15 and 21 in the midostaurin and placebo arms, respectively). [C0008]

The most-frequent treatment-related grade 3–4 AEs were thrombocytopaenia, neutropaenia, anaemia and febrile neutropaenia. The events leading to discontinuation in more than one patient were dermatitis exfoliative, increased ALT, increased AST, decreased neutrophil count and renal failure in the midostaurin group, and febrile neutropaenia and decreased neutrophil count and decrease platelet count in the placebo group. Overall, 23 (6.7%) patients in the midostaurin group and 17 (5.1%) patients in the placebo group discontinued therapy because of grade 3–4 AEs. [C0008]

Based on the safety results from the IIT trial, the treatment-related AEs and their severity were similar in patients aged ≤60 years and those aged >60 years. The incidence of SAEs and discontinuation because of AEs were higher in older patients. Deaths occurred at a higher frequency in patients aged >60 years. [C0008]

Grade 3–4 AEs occurring more frequently in the midostaurin group than in the placebo group were exfoliative dermatitis and device-related infections. Furthermore, an increased frequency of QTc prolongation has been observed in patients receiving midostaurin. A mechanistic explanation for this observation was not found. [C0008]

Table S.0.1: Summary of key results

Outcome	Anticipated absolute effects		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with midostaurin with standard induction and consolidation chemotherapy	Risk with standard induction and consolidation chemotherapy				
OS	1-year survival: 760 per 1000 3-year survival: 540 per 1000 5-year survival: 510 per 1000	1-year survival: 680 per 1000 3-year survival: 470 per 1000 5-year survival: 430 per 1000	HR 0.77 [0.63–0.95]	717 (1)	High	Indirect results comparing daunorubicin 90 mg/m^2 in the first induction cycle ("10 + 3" regimen) followed by a second course and consolidation versus midostaurin plus standard induction ("7 + 3" regimen) and consolidation, showed no difference between the treatments in terms of OS (HR=0.84 [95% CI: 0.54–1.31]).However, serious limitations apply to this indirect comparison. These include limited similarity of the treatments in the reference arms, difference in the follow-up times and partly unknown characteristics of the patient population in the FLT3 positive subgroup of UK NCRI AML 17 trial.
OS, censored for SCT	1-year survival: 820 per 1000 3-year survival: 650 per 1000 5-year survival: 640 per 1000	1-year survival: 700 per 1000 3-year survival: 580 per 1000 5-year survival: 560 per 1000	HR 0.75 (0.54–1.03)	717 (1)	High	
EFS	1-year survival: 470 per 1000 3-year survival: 320 per 1000 5-year survival: 310 per 1000	1-year survival: 330 per 1000 3-year survival: 230 per 1000 5-year survival: 210 per 1000	HR=0.73 (0.61–0.87)	717 (1)	High	
DFS (from first CR)	1-year survival: 700 per 1000 3-year survival: 490 per 1000 5-year survival: 480 per 1000	1-year survival: 540 per 1000 3-year survival: 380 per 1000 5-year survival: 360 per 1000	HR=0.66 (0.52–0.85)	717 (1)	High	
CR (all CRs occurring during induction)	650 per 1000	580 per 1000	RR=1.12 (1.00–1.26)	717 (1)	High	
CIR	—	—	HR=0.68 (0.52–0.89)	717 (1)	High	
Death as SAE **SAE** **Grade 3–4 AEs**	43 per 1000 470 per 1000 997 per 1000	63 per 1000 487 per 1000 1000 per 1000	—	717 (1)	Not assessed	Deaths on treatment includes those occurring within 30 days of discontinuation of treatment.

Outcome	**Anticipated absolute effects**		**Relative**	**Number of**	**Quality**	**Comments**
Grade 3–4 AEs suspected to be related to treatment	780 per 1000	752 per 1000				Grade 3–4 exfoliative dermatitis and device-related infections occurred more frequently in midostaurin-treatment group QTc prolongation has been observed in patients receiving midostaurin
Withdrawal because of grade 3–4 AEs	61 per 1000	45 per 1000				
HrQoL	Not available	Not available	Not available			

Abbreviations: see List of abbreviations.

Discussion

Scope of the assessment

The following treatments were considered the most-relevant comparators: (i) standard induction and consolidation chemotherapy (cytarabine in combination with daunorubicin 60 mg/m^2/day during the induction phase); and (ii) induction and consolidation chemotherapy with daunorubicin 90 mg/m^2/day during the induction phase. [B0001]

SCT, azacitidine and gemtuzumab ozogamicin (GO) were identified as potential treatment options (comparators) during the early scoping for this assessment. However, these comparators were excluded from the assessment because: (i) azacitidine is used in patients who are not suitable for intensive chemotherapy and, thus, this does not represent the patient group that was defined in the scope of this assessment; (ii) SCT is widely used for patients with AML who are suitable for SCT. However, because midostaurin and SCT treatments are not mutually exclusive treatment options, SCT was not included in PICO. SCT is considered for all eligible patients irrespective of the use of midostaurin; and (iii) GO was considered by the MAH as a relevant comparator because it has been prescribed in France as part of a compassionate-use program since 2014 [1]. However, it was not considered in this assessment as a relevant comparator because of its limited use in selected patients in only one member state.

Effectiveness

Midostaurin in combination with standard induction and consolidation chemotherapy improved OS in patients aged 18–60 years who were fit for chemotherapy. However, because of a plateau effect in the OS curves, the absolute OS gain was difficult to determine reliably. SCT is unlikely to significantly confound the effect of midostaurin on OS, despite the high rate of patients receiving SCT. Overall, key secondary outcomes support the conclusions based on the primary outcome (OS). No data on the health-related quality of life or disease-specific quality of life were available, which is a severe evidence gap. [D0001] Hower, according to MAH, quality of life data are being collected in the IIT and this data will become available once the study is completed.

There was no relevant heterogeneity in the effect on OS observed in the subgroup analyses, except for a difference between males and females. This difference was not fully discussed in the submission file. [D0001] This heterogeneity was not observed in other efficacy endpoints.

Based on the indirect comparison of midostaurin in combination with standard induction ("7 + 3 regimen") and consolidation chemotherapy versus high-dose (90 mg/m^2) daunorubicin induction ("10 + 3 regimen") and consolidation chemotherapy, there was no evidence that midostaurin treatment was more beneficial than high-dose daunorubicin used during induction, or vice versa. However, serious limitations apply to this indirect comparison. These include limited similarity of the treatments in the reference arms, difference in the follow-up times and partly unknown characteristics of the patient population in the FLT3 positive subgroup of UK NCRI AML 17 trial. Risk of bias at study and outcome level was also observed related to UK NCRI AML 17 trial subgroup analysis. Furthermore, the high-dose daunorubicin used during induction does not represent the gold standard of treatment across Europe.

Safety

Overall, AEs were balanced between the patient groups, although rates of grade 3–4 AEs were high. However, this is a typical outcome, given the health condition of the patients in these trials. Grade 3–4 AEs emerging more frequently in the midostaurin group than in the placebo group were exfoliative dermatitis and device-related infections. Furthermore, QTc prolongation has previously been observed in patients receiving midostaurin. [C0008]

Ethical, organisational, social and legal aspects

No potential concerns were identified in terms of ethical, organisational, social or legal aspects that would be related to using midostaurin with standard induction and consolidation chemotherapy. All patients receiving midostaurin must be tested for FLT3 mutation. However, this testing is not currently implemented Europe-wide, which could impact the use of this treatment in some countries.

Applicability and quality of evidence

Overall, evidence for the OS effect of midostaurin with standard induction and consolidation chemotherapy versus standard induction and consolidation chemotherapy alone was based on only one appropriately designed and analysed RCT with a low risk of bias. The direct evidence is of high quality. However, the indirect comparison of midostaurin has several limitations and the overall quality of evidence is low. Given the design of the RATIFY trial, the disposition of patients and the complex treatment regimen overall, the effects of midostaurin during continuation therapy are difficult to assess reliably. Only a small proportion of patients received midostaurin as continuation therapy.

RCT evidence was only available for patients aged 18–60 years (45.2 years on average), which was younger than patients typically treated in clinical practice across Europe. In addition, the proportion of patients undergoing SCT in the RATIFY trial is likely to be higher than those treated in clinical practice. This might be a reflection of a younger and healthier patient population recruited in the clinical trial. There is only limited evidence from patients over 60 years of age and this is based on a single-arm trial. By contrast, given these results, there is no reason to suspect that patients aged 60 years or more would not benefit from midostaurin. Instead of age, patient's fit for chemotherapy is more critical in terms of their eligibility for treatment. However, there is a clear evidence gap concerning the effects of midostaurin in older patients and the effect size in this population remains unknown.

Another issue related to the applicability of the results is the variation in the standard induction and consolidation chemotherapy regimens used across countries and regions. The most common therapies for AML comprise a combination of an anthracycline and continuous infusion of cytarabine and/or stem cell transplantation, depending on the risk group. Several anthracyclines at different dosages are recommended for use across Europe (e.g., idarubicin). Mitoxantrone can be also used instead of daunorubicin. Midostaurin has been studied in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and with patients in complete response followed by midostaurin monotherapy. There is no evidence of the effects of midostaurin in combination with other induction and consolidation alternatives except those used in the RATIFY trial. In addition, the indication of midostaurin is restricted to specific induction and consolidation chemotherapy.

Conclusion

Based on the results of this assessment, midostaurin in combination with standard induction and consolidation chemotherapy is considered to be more effective than standard induction and consolidation chemotherapy alone. More uncertainty is related to the beneficial effects of midostaurin used in continuation therapy because of patient disposition in the trials assessed, leading to fewer patients receiving continuation therapy. Based on indirect comparison, there was insufficient evidence to determine whether midostaurin treatment was more beneficial than high-dose daunorubicin (90 mg/m^2) used during induction in terms of OS. Serious limitations apply to this comparison. Patients over 60 years of age have not yet been studied in an RCT setting and the effect size of midostaurin on OS is unknown in this older population. However, it is the suitability of patients for intensive chemotherapy, rather than their age, which is the limiting factor to midostaurin use.

The safety profile of treatment with midostaurin in combination with standard induction and consolidation chemotherapy is considered to be comparable to standard induction and consolidation chemotherapy. However, grade 3–4 exfoliative dermatitis and device-related infections occurred more frequently in patients receiving midostaurin. Furthermore, QTc prolongation has been observed in patients receiving midostaurin. Deaths during the study treatment and 30-day follow-up periods occurred more frequently in patients over 60 years of age compared with those who were younger.

Further research is required on the effects of midostaurin in the older population. Health-related quality of life and disease-specific quality of life should be studied, because this evidence is currently lacking.

1 SCOPE

Description	Project scope
Population	Adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive. ICD-10: C92.0 Mesh-terms: Leukaemia, Myeloid, Acute Tree Number(s): C04.557.337.539.275 MeSH Unique ID: D015470
Intervention	There are three parts to the intervention: 1) induction therapy, 2) consolidation therapy and 3) continuation therapy. Eligible patients may receive SCT. **1) Induction therapy:** • cytarabine 200 mg/m^2/day intravenously on days 1–7. • daunorubicin 60 mg/m^2/day intravenously on days 1–3. • midostaurin 50 mg (two 25-mg capsules) twice daily orally on days 8–21. **2) Consolidation (four remission consolidation cycles):** • high-dose cytarabine 3 g/m^2 every 12 h on days 1, 3 and 5. • midostaurin 50 mg (two 25-mg capsules) twice daily orally on days 8–21. • dexamethasone 0.1% or other corticosteroid ophthalmic solution 2 drops to each eye once daily to begin 6–12 h before initiation of cytarabine infusion and to continue for at least 24 h after last cytarabine dose. **3) Continuation therapy:** • midostaurin 50 mg (two 25-mg capsules) orally twice daily for 28 days. Each cycle will be 28 days in length. Continuation therapy will continue until relapse or for 12 cycles maximum. **Note:** In clinical practice, variations might occur in the induction and consolidation therapy. For example, idarubicin might replace daunorubicin as an anthracycline, dose of cytarabine might vary both in the induction and consolidation therapy. Depending on line of the induction and consolidation therapy (i.e., first induction, second induction etc.), variations might occur and mitoxantrone might be added during the second induction or third consolidation. **MeSH terms:** midostaurin (MeSH Unique ID: C059539)
Comparison	• standard induction and consolidation chemotherapy (see above). Eligible patients might receive SCT. • induction and consolidation chemotherapy, except daunorubicin 90 mg/m^2/day (instead of 60 mg/m^2/day) is used in induction. • Maintenance therapy: placebo.
Outcomes	**Overall survival (OS)** **Overall survival (OS) censored at SCT**: censoring patients who receive a stem cell transplant at the time of the transplant. **Event-free survival (EFS)**: defined as the time from randomisation until the earliest qualifying event, including: failure to obtain a CR during induction; relapse; or death from any cause. **Disease-free survival (DFS)**: defined as the time from documentation of first CR at any time to the first relapse or death from any cause in patients who achieved a CR. **Complete remission rate (CR)**: the percentage of patients who achieved a complete response (CR). CR is defined as normalisation of blood counts and a bone marrow sample showing less than 5% blasts **Cumulative incidence of relapse (CIR)**: the percentage of patients who relapsed (a bone marrow sample showing more than 5% blasts) after achieving CR. **Proportion of patients who discontinued the treatment**: the percentage of patients who discontinued the treatment based on the reason for discontinuation (e.g., failure to achieve complete remission, relapse, adverse event, etc.). **Health-related quality of life (HRQL)**: generic and disease-specific HRQL **Adverse events (AEs)**: any AEs, serious AEs (SAE), Grade ≥3 AEs, Discontinuation because of AE, death as SAE, AE of special interest. **Note!** Additional outcomes may be considered based on data presented in the submission or CSR.

Abbreviations: see List of abbreviations.

2 METHODS AND EVIDENCE INCLUDED

The objective of the literature review was to identify studies related to the beneficial and harmful effects of midostaurin and its relevant comparators for the treatment of patients with newly diagnosed FLT3 mutation-positive AML who are fit for chemotherapy (see Scope). The manufacturer provided a systematic literature review of the evidence, which was critically assessed by members from the assessment team. The approach used by MAH is characterised in sections 2.3–2.5.

2.1 Assessment team

FIMEA acted as the main author, and was responsible for writing the clinical effectiveness and safety domains, including the discussions related to these domains. NOMA acted as the co-author and was responsible for writing the technical characteristics and health problem and current use domains, including the discussions related to these domains.

Dedicated reviewers (AEMPS, ZINL, TLV, NICE, HAS and IQWIG) reviewed the drafts of the project plan and the assessment report and commented on the presubmission material. IQWIG contributed only to reviewing information retrieval.

2.2 Source of assessment elements

The assessment elements are defined in the from HTA Core Model version ‘Rapid Relative Effectiveness Assessments (4.2)’.

2.3 Search

Objectives of MAH’s systematic literature search

The literature search was performed by MAH and was included in the submission. The search was performed to answer the following questions:

What published, or unpublished, randomised, controlled trials (RCTs) of induction therapies – either licensed in Europe, recommended by European guidelines or agents in development compared to a recommended therapy – have been conducted, or are ongoing, for use in patients with newly diagnosed (previously untreated) FLT3 mutation-positive AML who are fit for intensive chemotherapy?

What are the current guidelines in Europe or the US for standard of care for induction and consolidation therapy in patients with AML who are fit for intensive chemotherapy?

Eligibility criteria in MAH’s literature search

MAH selected studies for inclusion based on the criteria presented in Table 2.1 and Table 2.2.

Table 2.1. Systematic review inclusion criteria used in the MAH's systematic literature review

Characteristic	Inclusion criteria
Publication type	Original articles Errata
Languages	Any EU language
Population	Adults (≥18 years) with newly diagnosed FLT3-mutated AML fit for intensive chemotherapy [AML includes non-APL AML, acute erythroid leukaemia/Di Guglielmo syndrome and acute monocytic or monoblastic leukaemia]
Interventions	Induction therapy (first or second induction), with or without HGFs, with an agent either licensed in Europe, recommended by European guidelines or agents in development compared with a recommended therapy Anthracycline (idarubicin 10–12 mg/m^2 or daunorubicin 45–90 mg/m^2) + cytarabine 100–200 mg/m^2/day: 7+3 or 10+3 or 5+2 regimens eligible Mitoxantrone 12 mg/m^2 First-generation FLT3i (SOR, Rydapt®, LEST) Second-generation FLT3i (QUIZ, CREN, GILT) GO Studies following up patients after induction through consolidation therapy were also eligible.
Comparator	Induction therapy with standard-of-care chemotherapy recommended by European guidelines or placebo/no chemotherapy, with or without follow-up through consolidation therapy
Outcomes	OS EFS Rate of CR DFS RFS Rate of SCT Duration of treatment Treatment-related mortality On-treatment deaths Early death Infectious complications Treatment interruptions or dose changes Discontinuation (any cause) Discontinuation (because of AEs) SAEs (irrespective of whether possibly drug related) SAEs (possibly drug related) Grade 3–4 toxicities Grade 3–5 toxicities HrQoL Quality of complete response (e.g., minimal residual disease negative) Leucopoenia – anaemia, WBC count, absolute neutrophil/neutropaenia Severe infections: incidence density of (any) infections, malaria, tuberculosis, viral hepatitis, hepatitis C virus, pneumonia, blood infections, gastrointestinal infections, lung infections, invasive lung infection Pulmonary toxicity: pleural effusion, interstitial lung disease, pneumonitis Cardiac dysfunction/failure: LVEF change from baseline
Study design	Completed RCTs and ongoing RCTs (phase II[a], III or IV) Current European guidelines from 2006[b] or recent reviews (for reference cross-checking and identification of guidelines)
Date limits	Unlimited

Abbreviations: see List of abbreviations.

Table 2.2. Systematic review exclusion criteria used in the MAH's systematic literature review

Characteristic	Exclusion code and criterion
Publication type	• Not an original article
Duplicate	• Duplicate/copy
Languages	• Not an EU language
Population	• Paediatric disease (<18 years) • Acute promyelocytic leukaemia • Acute mast cell leukaemia • Myelodysplastic syndrome • Chronic myeloid leukaemia • Relapsed/refractory/drug-resistant disease • Patients randomised within first remission • Preleukaemic syndromes/myeloproliferative neoplasm/syndromes not transformed into AML • Down syndrome • Acute megaloblastic leukaemia • Core binding factor AML • Animal studies
Mixed populations	• Mixed child/adult population or mixed AML/other population with <80% of patients from the population of interest *and* subgroup data not reported
Interventions	• Patients randomised to intervention at consolidation, post remission, peri- or post HSCT or at maintenance stage of therapy • Intervention neither a current SoC in Europe nor a new agent/dose in development • Radiation • Azacitidine
Comparators	• Comparator not a SoC in Europe according to treatment guidelines • Radiation
Outcomes	• Does not include outcome listed in Table 2.1 • Outcomes reported only for the pooled treatment arms (not for each arm individually) were excluded, but tagged (listed in report) • No numeric data reported (tagged and listed in report)
Studies	• Not RCTs or guidelines • Observational study (e.g., cohort, case-control, database study) • Pilot study (even if RCT) • Study not intended to be powered to detect a statistically significant difference between treatment arms for the primary endpoint (even if RCT) • Single-arm studies • Case reports • Case series • Expanded treatment protocols • Expanded access programs • Phase I trial • Phase I/II trial *and* the publication reports only phase I data • Studies validating the real-world effects of implementing guidelines from any European country were excluded, but tagged

Abbreviations: see List of abbreviations.

Information sources and search strategy in MAH's literature search

The following electronic databases were included in the MAH literature search: Embase, via the Embase.com platform; the Cochrane Library database Central Register of Controlled Trials; Medline and Medline InProcess and electronic publications ahead of print via PubMed; clinicaltrials.gov, WHO (International Clinical Trials Registry Platform meta-registry) and European (EU Clinical Trials Register) registries. Hand-searches included conference proceedings for American Society of Hematology 2016 and European Hematology Association 2016/17 (searched for abstracts and e-posters) and reference lists of included publications and further hand-searching as summarised in Appendix 1. Search strings and strategies are also included in Appendix 1. The final search of databases was performed on 7th June 2017 and final congress searches were performed on 26th June 2017. The search protocol was included as part of the submission.

Authors' view on the search performed by MAH

Overall, the reporting of the search followed the requirements of the EUnetHTA guidelines and reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) statement [2]. The search covered the relevant databases and was conducted approximately 2 months before the start of the assessment, and can be considered up to date.

During the review, it was noted that MAH literature search on study registries might not be sensitive enough to find all eligible studies, and consequently it was uncertain whether the evidence base is complete. The study pool of midostaurin was checked by the authors with a handsearch in ClinicalTrials.gov 5.9.2017. No further relevant studies could be identified.

2.4 Study selection

Selection process used in MAH's literature review

First-pass screening on the basis of title/abstract was performed by MAH as per the eligibility criteria (Table 2.1 and Table 2.2) using the following steps: screening of the references by title/abstract, a revisit to all the 'Excludes' by another analyst to ensure the inclusion of all relevant studies, and senior review for authentication of the results and resolution of the queries. Full papers were reviewed by two researchers independently to confirm their eligibility. Uncertainties were discussed with an adjudicator and resolved. Where a paper remained borderline, a third appropriate reviewer would adjudicate. The primary publication for any study was taken as the first full paper reporting the primary outcome. Other citations for the same study were termed 'linked' citations. Linked citations that offered no unique information or that were superseded by either earlier or later publications were excluded during screening. Linked citations offering unique information were included and reported in a table, indicating which unique data were reported. A PRISMA diagram for the systematic literature search performed by MAH is presented in Figure 2.1.

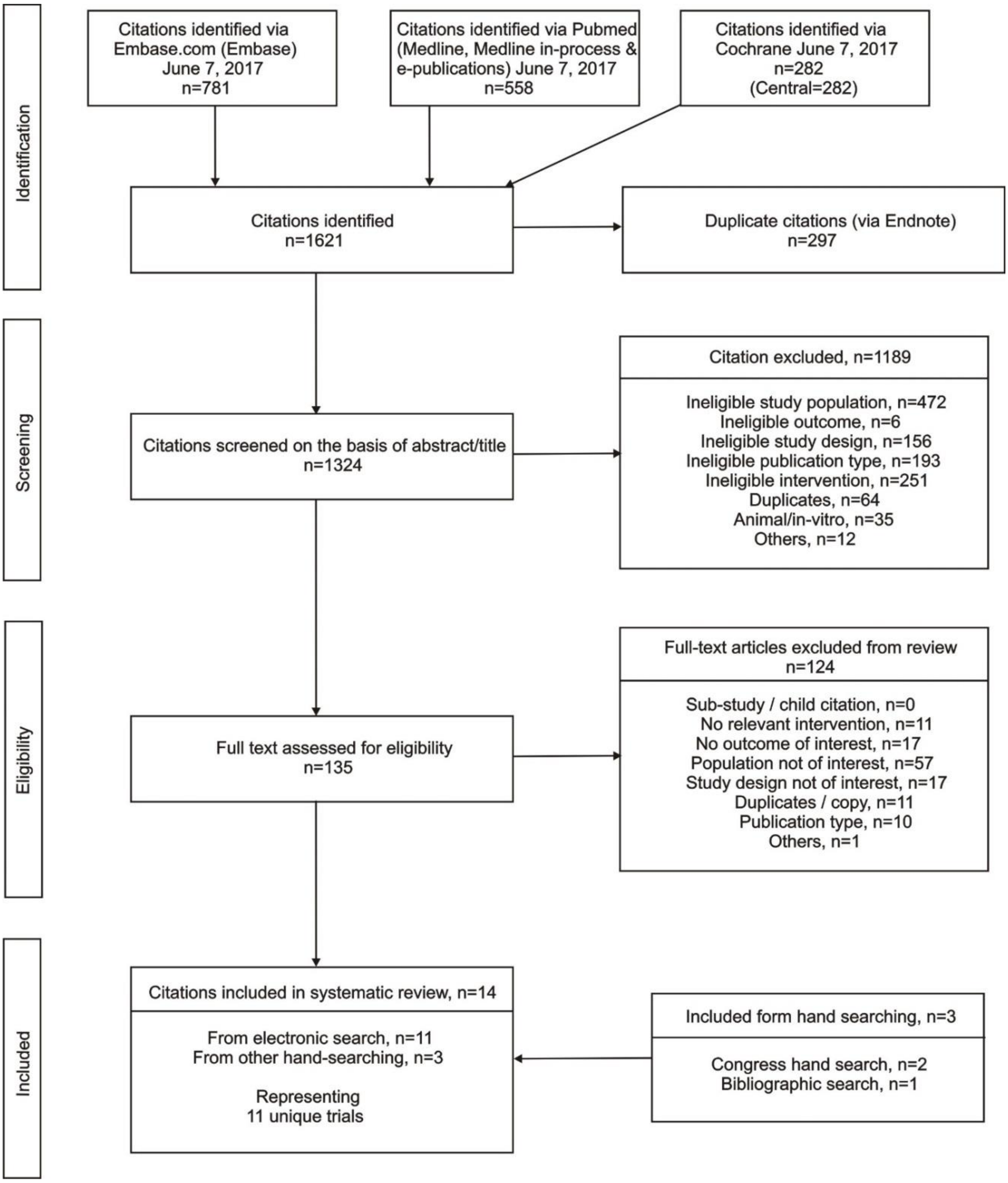


Figure 2.1. PRISMA diagram for the systematic literature search.

Characteristics of studies found in the literature review

In total, 11 RCTs reporting results were identified Table 2.3. Short et al. [3] did not report results and this study is not listed in Table 2.3. One study investigated therapy specifically in patients with FLT3 mutation-positive AML. This was a phase III study reporting the efficacy and safety of midostaurin in combination with daunorubicin and cytarabine. Results of this study were reported in [4]. Further details were provided to authors during the MAH submission, including CSRs. One study did not report its results. The remaining nine studies reported data for subgroups of patients with FLT3 mutation-positive tumours.

Table 2.3. List of relevant publications found in the literature search

Reference	Interventions	Number of FLT3 patients
RATIFY **[4]** **(CALGB 10603/ CPKC412A2301)**	**Intervention:** Midostaurin with standard induction and consolidation therapy followed by maintenance therapy with midostaurin **Comparator** As above, but placebo instead of midostaurin	Midostaurin: n=360 Placebo: n=357
[5] **(ECOG E1900 trial)**	**Induction** • D 90 mg/m²+C (100 mg/m²) (7+3) • D 45 mg/m²+C (100 mg/m²) (7+3) **Consolidation** • Allo-SCT or • HDAC (3 g/m² every 12 h every other day for a total of 6 doses) ± GO (single dose, 6 mg/m²) followed by SCT	FLT3-ITD D 90 mg: n=64 D 45 mg: n=83
[5, 6]	**Induction** • D 90 mg/m²+C (100 mg/m²) • D 45 mg/m²+C (100 mg/m²) **Consolidation** • Allo-SCT or • HDAC (3 g/m² every 12 h every other day for a total of 6 doses) ± GO (single dose, 6 mg/m²) followed by SCT	As for [5]
[7] **(ALFA-0701 trial)** **Median follow-up: 14.8 months**	**Induction** • D 60 mg/m²+C (200 mg/m²) (7+3)+GO (3mg/m²) • D 60 mg/m²+C (7+3) **Second induction** • D 60 mg/m²+C (1g/m²) (7+3)+G-CSF **Consolidation** • D 60 mg/m²+ C (7+3)±GO (6 mg/m²)	FLT3-ITD D + C (7+3) + GO: n=22 D + C (7+3): n=27
[8] **(Analysis of karyotyping data of *ALFA-0701 trial* reported in [7])**	As for [7]	**All patients** FLT3-ITD: n=49 D + C + GO: =22 D + C: n= 27 FLT3-TKD: n=14 D + C + GO: n= 10 D + C: n=4 **CN AML** FLT3-ITD: n=36 D + C + GO: n=16 D + C: n=20 FLT3-TKD: n=5 D + C + GO: n= 3 D + C: n= 2
[9] **(UK NCRI AML15 trial)**	**Induction** • ADE (D 50 mg/m²+C 100 mg/m²+E 100 mg/m²) (10+3+5) ± GO 3 mg/m² • D 50 mg/m²+C 100 mg/m² (3+10)±GO • FLAG-Ida±GO 3 mg/m² **Second induction** • ADE (D 50 mg/m²) (8+3+5) • D 50 mg+C (3+8) • FLAG-Ida (F 30 mg/m²+C 2 g/m²+G-CSF+I 8 mg/m²) **Consolidation** • MACE/MidAC (A 100 mg/m²+C 200 mg/m²+E 100 mg/m² then M 10 mg/m²+C 1.0 g/m²)±GO 3 mg/m² • C (1.5 g/m²)±GO 3 mg/m² • C (3 g/m²)±GO 3 mg/m²	FLT-ITD **Induction** ADE: n=72 D + C: n=63 ADE: n=37 FLAG-Ida: n=34 **At consolidation randomisation:** MACE/MidAC n=37 C (any dose): n=45 C (3 g, adults): n=24 C (1.5 g): n=21 **4 courses**: n=9 **5 courses**: n=5
[10] **(UK NCRI AML17 trial)**	**Course 1** • D 90 mg/m²+C (100 mg/m²) • D 60 mg/m²+C (100 mg/m²)	FLT3-ITD D 90 mg: n=100 D 60 mg: n=100

Reference	Interventions	Number of FLT3 patients
	Course 2 • D 50 mg/m^2+C (100 mg/m^2)+LEST • D 50 mg/m^2+C (100 mg/m^2)+P **Course 3** • C 100 mg/m^2±LEST/Ev **Course 4** • LEST ± Ev • C 100 mg/m^2±LEST/Ev	
[11] **(Update of NCRI AML 17 trial, median follow-up of 28 months)**	As for [10]	As for [10]
[12] **UK NCRI AML16 trial**	**Induction** • D 50 mg/m^2+Cl 20 mg/m^2±GO 3 mg/m^2 • D 50 mg/m^2+C 100 mg/m^2 (3 + 10)±GO mg/m^2 **Induction 2** • D 50 mg/m^2+Cl • D 50 mg/m^2+C 100 mg/m^2 (3+8) **Consolidation** • D 50 mg/m^2+C 100 mg/m^2 (2+5) • No consolidation **Maintenance** • Aza 75 mg/m^2 • No consolidation	FLT3-ITD D + Cl + GO: n=18 D + C: n=14
[13]	**Induction** • D 60 mg/m^2+C 100 mg/m^2 (7+3) **Second induction** • D 60 mg/m^2+C-dose intermediate (1 g/m^2) (7+3)+S (400 mg BID)±P **Consolidation** • C (1 g/m^2)	FLT3-ITD S: n=15 P: n=13
[14]	**Induction** • D 60 mg/m^2 + C 100 mg/m^2 (3+7) + S 400 mg BID • D 60 mg/m^2 + C 100 mg/m^2 (3+7) + P **Second induction** • D 60 mg/m^2 + C (3+7) + S ± HAM (C 3 mg/m^2, M 10 mg/m^2) • D 60 mg/m^2 + C (3+7) + P ± HAM **Consolidation** • C (3 g/m^2) + S • C (g/m^2) + P **Maintenance** • S or P	FLT3-ITD S: n=23 P: n=23
[15]	**Induction** • I 12 mg/m^2 + C 200 mg/m^2 (3+7) • D 90 mg/m^2 + C 200 mg/m^2 (3+7) **Second induction** • I 12 mg/m^2 + C 200 mg/m^2 (2+5) • D 45 mg/m^2 + C 200 mg/m^2 (2+5)	FLT3-ITD I + C, n=27 D + C, n=17
[16]	**Induction** • CPX-351 100 units/m^2 (3) • D 60 mg/m^2+C 100 mg/m^2 (3+7) CPX-351 is nano-scale liposomal formulation of 5:1 molar ratio C and D	FLT3-ITD/TKD, n=44 ITD, n=33 TKD, n=17

Abbreviations: see List of abbreviations.
Source: adapted from [17].

Studies included in the assessment

According to MAH, only one RCT (RATIFY) was considered directly relevant for the assessment, because daunorubicin 60 mg/m^2 plus cytarabine as induction therapy followed by high-dose cytarabine is considered the main European standard of care and therefore the most relevant comparator to midostaurin-based therapy, based on current treatment guidelines.

However, in this assessment, induction and consolidation chemotherapy with high-dose daunorubicin (90 mg/m^2/day instead of 60 mg/m^2/day) in induction was also considered as a relevant comparator (see section 1, Scope). Consequently, UK NCRI AML17 trial (RCT), including its updated results, were considered relevant to this assessment by the authors and were included in the analyses in addition to the RATIFY trial. In the UK NCRI AML17 trial [10, 11], high-dose daunorubicin was compared with standard-dose daunorubicin used in induction. All the other RCT studies found in the systematic literature review, except the RATIFY and UK NCRI AML17 trials, were excluded from analyses because of the lack of relevant comparisons.

Aside from the literature review for RCTs, a single-arm investigator-initiated trial (AMLSG 16-10, referred to as the IIT trial) reported results on the efficacy and safety of midostaurin added to daunorubicin plus cytarabine in patients with newly diagnosed FLT3-ITD mutation-positive AML. This study involved patients aged 18–70 years and provides supporting data, particularly relating to the efficacy and safety of midostaurin in older patients.

The details and results of IIT trial are included in the submission file. The authors conducted a hand-search of clinical trials.gov to find any phase II–III interventional studies with midostaurin in AML. No other relevant single-arm studies with results were found, except for the IIT trial. The results of the IIT trial were mainly used to characterise the effects in older patients.

The study selection for studies included in the assessment is presented in Figure 2.2. Details and references can be found in Table 2.3 and Table 2.4.

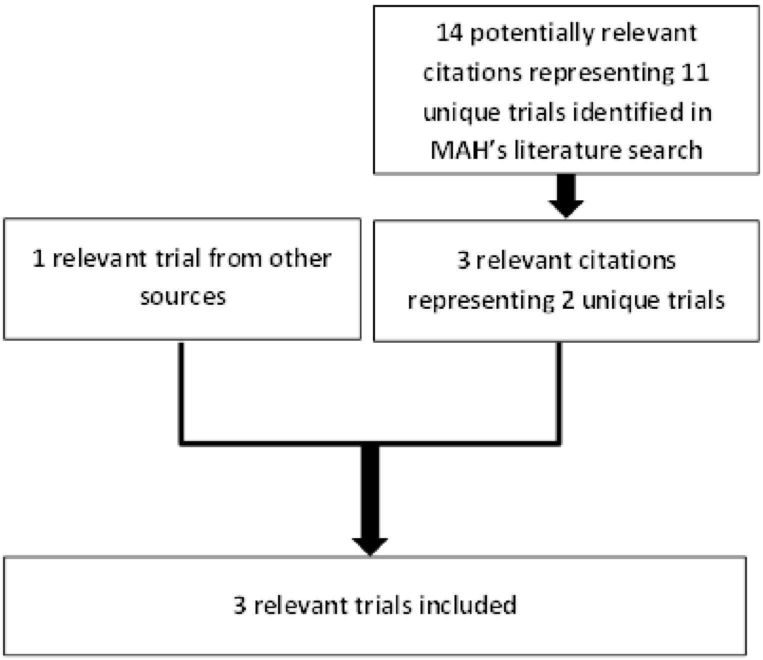


Figure 2.2. Selection of studies included in the assessment. The final selection was conducted by the EUnetHTA authors.

2.5 Data extraction and analyses

Data extraction

In the MAH submission, details of the data collection process, outcome prioritisation and plans for data synthesis were not explicitly stated, as required in PRISMA-P.

The data and results for the RATIFY and IIT studies were included in the MAH submission file. MAH presented these data as in the CSR. Results for the UK NCRI AML17 [10, 11] trial were extracted from the publications by the authors.

Data synthesis and analyses

Direct comparisons were represented as in the MAH submission file. Indirect comparison of midostaurin with standard induction and consolidation therapy versus induction and consolidation chemotherapy with high-dose daunorubicin (90 $mg/m^2/day$) during induction was performed by the authors using the Bucher method according to the EUnetHTA guideline [18].

2.6 Quality rating

Risk of bias assessment was conducted at the study and outcome levels for RCTs by the authors. GRADE was used to assess the quality of evidence by the authors. See Appendix 1 for details.

2.7 Patient involvement

After consultation with patient organisations, a Romanian patient with AML was identified. An open interview, based on the HTAi questionnaire template, was conducted with this patient. The experiences of the patient informed the outcomes taken into consideration for this Joint Assessment.

2.8 Description of the evidence used

Table 2.4. Main characteristics of studies included. Detailed data tables are included in Appendix 1

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
RATIFY (CALGB 10603/ CPKC412A 2301)	Phase III randomised, double-blind placebo-controlled study	Midostaurin (n=360) and Placebo (n=357)	**Intervention:** midostaurin with standard induction and consolidation therapy followed by maintenance therapy with midostaurin **Comparator:** as above, but placebo instead of midostaurin	OS Key secondary objective: EFS Other secondary endpoints: CR, DFS, CIR, OS, EFS and DFS censored at time of SCT	Yes
[10, 11] UK NCRI AML17 trial	Phase III randomised controlled trial	Daunorubicin 90 mg/m^2 n=604 (100 with FLT3 ITD) Daunorubicin 60 mg/m^2 n=602 (100 with FLT3 ITD)	**Intervention:** high-dose daunorubicin (90 mg/m^2) in induction **Comparator:** standard-dose daunorubicin (60 mg/m^2) Additional treatments described in Appendix 1.	Complete remission (CR) CR duration Relapse rate, monitored over 5 years Deaths in CR, monitored over 5 years Overall survival (at 5 years) Toxicity Quality of life Supportive care requirements	Yes (effectiveness as applicable)
Investigator-initiated trial (referred as the IIT trial in this document) AMLSG 16-10, CPKC412A DE02T [17, 19, 20]	Open-label, single-arm, phase II study	n=145	Midostaurin plus daunorubicin plus cytarabine	EFS Secondary outcome measures: CR RFS OS	Yes

Abbreviations: see List of abbreviations.

2.9 Deviations from project plan

Azacitidine was excluded from the list of relevant comparators. Azacitidine is used in patients who are not suitable for chemotherapy and thus do not represent the patient group that is defined in the scope of this assessment.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is midostaurin and its comparators?
A0020	What are the approved indications of midostaurin?
B0002	What is the claimed benefit of midostaurin in relation to its comparators in AML?
B0003	What is the phase of development and implementation of midostaurin and its comparator(s)?

3.2 Results

Features of the technology and comparators

[B0001] What is midostaurin and its comparators?

Midostaurin is an orally administrated staurosporine analogue with potent activity against both ITD- and TKD-mutant as well as wild-type FLT3. In addition, it also inhibits other molecular targets, including several isoforms of protein kinase C, KIT, VEGFR-1, FGFR and multidrug resistance gene products implicated in the pathogenesis of AML. Midostaurin inhibits FLT3–receptor signalling in leukaemic cells that express FLT3-ITD or TKD mutant receptors, leading to cell cycle arrest and apoptosis.

Several possible relevant comparators in the European setting were identified based on recommendations in guidelines [21-24]. The most common therapies across Europe comprise a combination of an anthracycline and continuous infusion of cytarabine in the classic '3+7' regimen (i.e. 3 days of intravenous administration of an anthracycline combined with 7 days of continuous intravenous cytarabine as induction chemotherapy), followed by consolidation therapy with intermediate or high-dose cytarabine-based chemotherapy, and/or stem cell transplantation, depending on the risk group.

Several anthracyclines at different dosages are used across European countries (e.g., idarubicin). Mitoxantrone can be used instead of daunorubicin, and high-dose daunorubicin 90 mg/m^2/day can be used during induction phase. High-dose daunorubicin has been recommended for example in Norway.

The most relevant comparators for this rapid assessment are as follows (

Table 3.1):

- Standard induction and consolidation chemotherapy (cytarabine in combination with daunorubicin 60 mg/m^2/day during the induction phase).
- Induction and consolidation chemotherapy, using daunorubicin 90 mg/m^2/day (instead of 60 mg/m^2/day) during the induction phase.

Daunorubicin is a cytotoxic antibiotic (anthracycline family) isolated from *Streptomyces coeruleo-rubidus.* Daunorubicin exerts its effects on cancer cells primarily through two mechanisms. Intercalation occurs when the drug wedges between the bases of DNA. This blocks DNA from being copied (replication) or being translated to make proteins. The drug also inhibits (reduces) the activity of an enzyme, topoisomerase type II. This leads to breaks in the genomic DNA.

Cytarabine is an analogue of pyrimidine, which is part of the genetic material of cells (DNA and RNA). In the body, cytarabine takes the place of pyrimidine and interferes with the enzymes involved in the production of new DNA. As a result, cytarabine slows the growth of tumour cells and eventually kills them. In DepoCyte, cytarabine is contained in liposomes (small fatty particles), from which the medication is slowly released.

Table 3.1. Features of the intervention and comparators

	Midostaurin	Cytarabine	Daunorubicin
Nonproprietary name	Midostaurin	Cytarabine	Daunorubicin
Proprietary name	Rydapt	Several proprietary names are used across Europe	Several proprietary names are used across Europe
Active substance	Midostaurin (PKC412)	Cytosine arabinoside (ara-C)	Daunorubicin hydrochloride
Galenic form	25-mg soft capsules	IV formulation	IV formulation
ATC code	L01XE39	L01BC01	L01DB02
VNR code	N/A	Several in use	Several in use

Abbreviations: see List of abbreviations.
Sources: [17, 25].

Table 3.2. Administration and dosing of the intervention and comparators

	Midostaurin	Cytarabine	Daunorubicin
Nonproprietary name	Midostaurin	Cytarabine	Daunorubicin
Administration mode	Soft capsules to be taken orally	IV, SC, IM	IV
Description of packaging	Capsules are packaged in PA/Al/PVC-Al blisters	Refer to relevant country SPC	Refer to relevant country SPC
Total volume contained in packaging for sale	Packs of 112 capsules of 25 mg, corresponding to 28 days of therapy. A 14-day pack with 56 capsules might also become available in some countries.	Refer to relevant country SPC	Refer to relevant country SPC
Recommended duration of treatment	See Table 3.3	See text below table	See text below table
Dosing	See Table 3.3	According to patient´s weight and/or body surface area	According to patient´s weight and/or body surface area
Contraindications	Concomitant administration of potent CYP3A4 inducers, e.g., rifampicin, St John's Wort (*Hypericum perforatum*), carbamazepine, enzalutamide and phenytoin. For patients with hypersensitivity to the active substance or to any of the excipients	Refer to relevant country SPC	Refer to relevant country SPC For patients with hypersensitivity to the active substance or to any of the excipients or to any other anthracyclines, older patients, patients with heart insufficiencies for patients previously treated with anthracyclines and who already have reached the cumulative maximal dose

Abbreviations: see List of abbreviations.
Sources: [1, 17, 25].

Recommended duration of treatments

Midostaurin

Based on data from the pivotal phase III trial, RATIFY, the median (mean) length of a course of therapy is 14 (14) days during induction cycles 1 and 2, 56 (41) days during consolidation and 336 (262) days during maintenance. Patients receive one or two 28-day cycles of induction therapy followed by one to four 28-day cycles of consolidation therapy. During the induction and consolidation cycles, patients achieving CR and not going on to have SCT then receive daily midostaurin maintenance monotherapy for up to 12 cycles.

Induction and consolidation therapy

According to international guidelines, the most common doses and regimen duration for cytarabine and daunorubicin are as follows:

Induction phase:

- Cytarabine 100–200 mg/m^2/day+daunorubicin (7+3 days)
- Cytarabine 100–200 mg/m^2/day+daunorubicin (5+2 days)
- Daunorubicin can be administrated as either 60 or 90 mg/m^2 day

Consolidation phase:

- High-dose cytarabine 3 g/m^2/day BID

STC should be considered for patients who are not suitable enough for HDCT. See Table 3.3 for more detailed information regarding treatment dosing and duration.

Table 3.3. Dosing of midostaurin

Method of administration	Oral
Doses	50 mg BID, at approximately 12-h intervals
Pack size	112 × 25-mg capsules A 14-day pack with 56 capsules might also become available in some countries
Dosing frequency	Days 8–21 of 28-day chemotherapy cycles (induction and consolidation) and daily during midostaurin maintenance monotherapy
Median length of a course of treatment (including induction, consolidation and maintenance)	Based on data from the pivotal phase III trial, RATIFY, the median (mean) length of a course of therapy was 14 (14) days during induction cycles 1 and 2, 56 (41) days during consolidation and 336 (262) days during maintenance. Overall, the median length of therapy was 42 (136) days. Only 33% of patients received maintenance therapy.
Anticipated average interval between courses of treatments	Patients receive one or two 28-day cycles of induction therapy followed by one to four 28-day cycles of consolidation therapy. During induction and consolidation cycles, midostaurin is given on days 8–21. Patients achieving CR and not going on to have SCT then receive daily midostaurin maintenance monotherapy for up to 12 cycles
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	<u>During all three phases of treatment:</u> • midostaurin dosing should be interrupted in cases of grade 3–4 pulmonary infiltrates for the remainder of the cycle and resumed when infiltrate resolves to grade ≤1 • midostaurin dosing should be interrupted in cases of other grade 3–4 nonhaematological toxicities considered at least possibly related to midostaurin and resumed when they have resolved to grade ≤2 • In cases of QTc interval >470 msec and ≤500 msec, midostaurin should be decreased to 50 mg OD for the remainder of the cycle and resumed at 50 mg BID in the next cycle provided that QTc interval improves to ≤470 msec at the start of that cycle. Otherwise, midostaurin should be continued at 50 mg OD • In cases of QTc interval >500 msec, midostaurin should be withheld or interrupted for the remainder of the cycle. If QTc improves to ≤470 msec just before the next cycle, midostaurin should be resumed at the initial dose. If QTc interval is not improved in time to start the next cycle, midostaurin should not be administered during that cycle. Midostaurin can be withheld for as many cycles as necessary until QTc improves <u>During maintenance therapy only:</u> • In cases of grade 4 neutropenia (ANC <0.5 × 10^9/L), midostaurin should be interrupted until ANC ≥1.0 × 10^9/L, and then resumed at 50 mg BID. If neutropenia (ANC <1.0 × 10^9/L) persists for >2 weeks and is suspected to be related to midostaurin, midostaurin should be discontinued • In cases of persistent grade 1/2 toxicity that patients deem unacceptable, midostaurin can be interrupted for up to 28 days

Abbreviations: see List of abbreviations.

[A0020] What are the approved indications of midostaurin?

Midostaurin is indicated:

- In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single-agent maintenance therapy, for adult patients with newly diagnosed AML who are FLT3 mutation positive;

- As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL).

This rapid assessment is limited to the AML indication.

[B0002] What is the claimed benefit of midostaurin in relation to the comparators in AML?

Midostaurin is the first targeted therapy, and the first tyrosine kinase inhibitor therapy, for patients with newly diagnosed FLT3 mutation-positive AML. Midostaurin added to induction and consolidation chemotherapy followed by midostaurin maintenance therapy (in patients not receiving SCT) is claimed to extend OS versus standard-of-care treatment. Furthermore, other outcomes such as event-free survival (EFS), disease-free survival (DFS), cumulative incidence of relapse (CIR) and proportion of patients achieving complete response (CR), after one cycle of induction therapy are claimed to support the results and conclusions based on primary outcome.

[B0003] What is the phase of development and implementation of midostaurin and the comparator(s)?

Recommended new text "Midostaurin gained the first regulatory approval worldwide from the US Food and Drug Administration (FDA) on 28th April 2017 and from Swissmedic on 4th May 2017 followed by Health Canada approval on 21st July 2017 and EU approval (EC decision) on 18th September 2017. While the FDA and Health Canada approvals were restricted to the induction and consolidation phase, the EMA and Swissmedic approvals included induction, consolidation and the maintenance phasesThe FDA approval was restricted to the induction and consolidation phase. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 20th July 2017.

Cytarabine and daunorubicin gained regulatory approval for use in AML before CP procedures were available.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is AML and the natural course of the disease? What is the impact of FLT3 mutation on prognosis and treatment choice?
A0003	What are the known risk factors for AML?
A0004	What is the natural course of AML?
A0005	What are the symptoms and burden of the disease or health condition for the patient?
A0024	How is AML currently diagnosed according to European published guidelines?
A0025	How is newly diagnosed AML currently managed in clinical practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

4.2 Results

Overview of the disease or health condition

[A0002] What is AML and natural course of the disease? What is the impact of FLT3 mutation on prognosis and treatment choice?

AML is a form of leukaemia (i.e., cancer of the white blood cells) characterised by infiltration of proliferative, clonal, abnormally differentiated and occasionally poorly differentiated haematopoietic cells of myeloid lineage in the bone marrow, blood and other tissues. The prognosis of patients with AML varies dramatically because of several prognostic factors: age, performance status, cytogenetic and/or molecular genetic alterations, including FLT3, NPM1 and CEBPA.

The annual crude incidence of AML is 3.7 per 100,000 and the number of new cases per year in Europe is estimated at 18,400. AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemias in adults in the Western world. The incidence of AML increases sharply with age, ranging from 1.8 cases per 100,000 people aged less than 65 years of age to 17.6 cases per 100,000 people over 65 years of age. More than half of patients with newly diagnosed AML in developed countries are over 65 years of age, with a median age at diagnosis of 67, and AML is more common in men than in women. [17, 26]

Genetic alterations in FLT3 in AML

Among the prognostic molecular alterations, one of the most important factors is the presence of FLT3 gene mutations, which occur in approximately 30% of adult patients with AML and have a substantial negative impact on prognosis [27]. FLT3 encodes a class III receptor tyrosine kinase that comprises five immunoglobulin-like domains, a transmembrane domain, a cytoplasmic juxtamembrane domain and two tyrosine kinase domains. FLT3 has a critical role in normal haematopoiesis and cellular growth in primitive haematopoietic stem and progenitor cells. Under normal conditions, FLT3 is expressed on bone marrow haematopoietic stem cells, but this expression is gradually lost as cells differentiate.

Mutant FLT3 is constitutively activated, which results in the proliferation and survival of leukaemic blasts. Two forms of FLT3-activating mutations are identified commonly in blasts from patients with AML: internal tandem duplications (ITDs) and point mutations, both of which can occur in the juxtamembrane domain or the tyrosine kinase domain.

FLT3-ITD mutations are observed in 20%–25% of patients with *de novo* AML and in 30%–35% of patients with cytogenetically normal newly diagnosed AML (~30% of all patients with AML). Point mutations of the FLT3 protein tyrosine kinase domain (FLT3-TKD mutations) are observed in 5%–10% of all patients with AML and in 11%–14% of patients with cytogenetically normal AML [28]. FLT3-TKD mutations have not been associated with a poor prognosis in some large studies [29].

The biology of AML can differ between young and older patients with AML, but not in the subset of patients with FLT3 mutations eligible for intensive chemotherapy. The main change in the biology of AML related to age is an increase in complex cytogenetics in older patients, which is not relevant to patients with a FLT mutation. Therefore there are no reasons to expect that the mode of action differs between older and younger patients with FLT3-positive AML. Whether midostaurin will have the same effect size in older patients as in those included in the RATIFY trial study is uncertain.

Other relevant genetic alterations in AML

Alterations in NPM1 can also affect the outcome of patients with AML. One-third of patients with AML can have a mutation in the NPM1 gene. Results from conventional cytogenetics and from NPM1, FLT3 and CEBPA mutational screening are used in routine practice following 2010 ELN recommendations [21]. The original intention of the ELN genetic categories was to standardize reporting of genetic abnormalities particularly for correlations with clinical characteristics and outcome. The prognostic impact of many markers is context dependent, with the effect of a given abnormality dependent on the presence and/or absence of another. Most recent studies suggest that patients with NPM1 mutation and FLT3-ITD with a low (0.5) allelic ratio (FLT3-ITDlow) have a similar (favourable) outcome as patients with a NPM1 mutation but no FLT3-ITD; thus, both groups are now considered to have a favourable outcome [19, 30-32]. By contrast, patients with AML with wild-type NPM1 and FLT3-ITD with a high (0.5) allelic ratio (FLT3-ITDhigh) have a poor prognosis and are placed in the adverse-risk group, although the panel acknowledges that the natural course of AML with FLT3 mutation might change with the use of FLT3 inhibitors (Table 4.1) [33]. Prognostic impact of a marker is treatment-dependent and may change with new therapies.

Table 4.1. ELN risk stratification by genetics. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data.

Risk category	Genetic abnormality
Favourable genetic group	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD ^{low*} Biallelic mutated CEBPA
Intermediate genetic group	Mutated NPM1 and FLT3-ITD ^{high*} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD ^{low*} (without adverse-risk genetic lesions) The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations. MLLT3-KMT2A Cytogenetic abnormalities not classified as favourable or adverse**
Adverse genetic group	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) 25 or del(5q); 27; 217/abn(17p) Complex karyotype*** and monosomal karyotype Wild-type NPM1 and FLT3-ITD ^{high*} Mutated RUNX1 inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* Mutated ASXL1# Mutated TP53#

* Semiquantitative assessment of FLT3-ITD allelic ratio (using DNA fragment analysis): low allelic ratio (< 0.5); high allelic ratio (≥ 0.5);

** For most abnormalities, it is not possible to draw firm conclusions regarding their prognostic significance due to a limited numbers studied

*** Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions. That is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3). This indicate how many complex karyotype cases have involvement of chromosome arms 5q, 7q, and 17p
# These markers should not be used as an adverse prognostic marker if they co-occur with favourable-risk AML subtypes.
Abbreviations: see List of abbreviations.
Source: [33]

For patients with AML, the 5-year survival rate is 19%. The mortality rate strongly correlates with age, for older patients (60 years and above) the 5-year survival rate is 3%–8%, whereas for younger patients (<60 years), the 5-year survival rate can be up to 50% [34]. The CR rate in patients with FLT3-mutated AML treated with standard first-line induction chemotherapy regimens is generally equivalent to that of patients without FLT3 mutations (78% vs. 82%) but median time to relapse, DFS, EFS and OS at 5 years are worse [30, 35-37]. For patients with FLT3-mutated AML who are <60 years of age and in first remission, the median time to relapse is estimated to be approximately 9 months, which is worse than the median 27 months to relapse for patients with FLT3 wild-type AML in the same age range [34, 35, 37].

[A0003] What are the known risk factors for AML?

Factors that might increase the risk for AML include [26, 33]:

- Age. The risk for AML increases with age. AML is most common in adults aged 65 and over.
- Gender. Men are more likely to develop AML than are women.
- Previous cancer treatment. Patients who have received certain types of chemotherapy and radiation therapy might have a greater risk of developing AML.
- Exposure to certain chemicals, such as benzene, is linked to greater risk for AML.
- Smoking.
- Other blood disorders. Patients who have had another blood disorder, such as myelodysplasia, polycythaemia vera or thrombocythaemia, are at greater risk of developing AML.

Prognostic factors in AML can be subdivided into those that are related to the patient and those that are related to the disease. Patient-associated factors (e.g., increasing age, comorbid conditions and poor performance status) commonly predict treatment-related early death, whereas disease-related factors (e.g., white cell count, prior myelodysplastic syndrome or cytotoxic therapy for another disorder, and leukaemic-cell genetic changes, including alterations in FLT3) predict resistance to current standard therapy. Alterations in FLT3 and/or in NPM1 can also affect the outcome of patients with AML. [30, 33, 38]

The patient's age or fitness (including performance status and the presence of comorbidities) and initial leukocyte count are considered important risk factors. Age or fitness influences survival and prognosis, in part related to the fact that initial treatment with intensive chemotherapy might not be tolerated by many older and/or less healthy patients.

History of previous cerebrovascular disease, rheumatological disease, psychiatric disease, and in particular, renal disease, have all been shown to affect and increase the risk for all-cause and cancer-specific mortality in patients with AML [39].

[A0004] What is the natural course of AML?

AML is a heterogeneous haematological malignancy. The term 'AML' refers to a group of haematopoietic stem cell disorders characterised by the overproduction of immature myeloid stem cells (blast cells or 'blasts'). The percentage of blasts in the bone marrow or blood is particularly important in defining AML and, according to current World Health Organization (WHO) criteria, the blast count for making a diagnosis of AML should generally exceed 20%.[40]

Current staging and classification systems for the condition recognise that there are two major aetiologies of AML: *de novo* and secondary or iatrogenic AML, resulting from exposure to chemotherapy or radiotherapy [41]. This assessment relates to *de novo* AML only. There are four main classifications of AML, namely: AML with recurrent genetic abnormalities; AML with myelodysplasia-related changes; AML not otherwise specified (NOS); and therapy-related myeloid neoplasms (secondary/iatrogenic AML). The most common subtype is AML NOS, with a 16.8 per 1,000,000 person-years incidence rate. [42]

Untreated AML is a fatal disease; median survival is 11–20 weeks, with mortality resulting from complications (such as serious infection and haemorrhage) that are associated with the fundamental bone marrow failure that defines this leukaemia [43]. Therefore treatment should be initiated as soon as possible, ideally within a matter of days after diagnosis [21]. Despite early intervention after diagnosis, induction chemotherapy might not help all patients achieve remission and as many as 50%–70% of those who do achieve remission following chemotherapy relapse within 3 years [38].

Effects of the disease or health condition

[A0005] What are the symptoms and burden of the disease or health condition for the patient?

The presenting early signs and symptoms of AML can be vague and nonspecific and might include fever, fatigue, pain, shortness of breath, cough, bleeding and bruising, pallor and persistent or frequent infections, but as many as one-third of patients can be asymptomatic at diagnosis.

Receiving a diagnosis of AML is traumatic, with little time for patients to adjust to their diagnosis before treatment needs to be initiated, and the current standard of care used in management of AML can have a significant impact on patient short-term and long-term health-related quality of life (HrQoL) [44, 45]. Patients report high rates of fatigue when receiving induction treatment. Furthermore, complications of the disease at presentation (such as anaemia, persistent infections and bleeding risk) and severe myelosuppression, which is a consequence of both the disease and of induction chemotherapy, negatively impact patients.

Caregivers also face burdens from living with, caring for and supporting a patient with AML, and find the period of supporting patients during chemotherapy a time of high burden, describing this period as disruptive [46]. Caregivers continue to face burdens across the patient treatment journey, and there are studies showing that when patients are undergoing SCT, caregivers experience particular mood disturbances and emotional distress, report a decline in physical functioning, general health and vitality, and note a negative impact on social functioning and family caregiving.[47, 48]

Current clinical management of the disease or health condition

[A0024] How is AML currently diagnosed according to European published guidelines?

The procedures used to diagnose and classify AML are:

- morphologic assessment of bone marrow specimens and blood smears (with ≥20% blasts in the bone marrow or peripheral blood being diagnostic of AML);
- analysis of the expression of cell-surface and cytoplasmic markers; and
- identification of chromosomal findings, and screening for selected molecular genetic alterations.

Currently, three molecular markers are used as part of standard clinical practice for risk stratification [21]:

- alterations in nucleophosmin-1 (NPM1);
- alternations in CCAAT/enhancer-binding protein alpha (CEBPA); and
- alterations in FLT3.

FLT3 mutation testing is required to identify patients for whom midostaurin is relevant. Currently, testing for FLT3-ITD is performed in some patients for prognosis. The introduction of midostaurin will necessitate the introduction of routine testing for both FLT3-ITD and FLT3-TKD by a validated test in a timely manner in all patients eligible to receive intensive chemotherapy.

Definitive diagnosis of AML requires examination of peripheral blood and bone marrow specimens to assess cell morphology and involves cytochemistry, immunophenotyping, cytogenetics and molecular genetics to describe the features of AML [26].

[A0025] How is newly diagnosed AML currently managed in clinical practice?

Although AML was incurable 50 years ago, it is now cured in 35%–40% of adult patients who are 60 years of age or younger and in 5%–15% of patients who are older than 60 years of age [21]. Treatment of AML is with curative intent whenever possible. In patients eligible for intensive induction chemotherapy, treatment comprises a combination of an anthracycline and continuous-infusion cytarabine in the classic '3+7' regimen (i.e., 3 days of intravenous administration of an anthracycline, combined with 7 days of continuous intravenous cytarabine). Current practice is that patients with AML who are older than 60 and otherwise fit should also be treated with standard induction and consolidation chemotherapy.

Once complete remission is achieved after intensive therapy, appropriate postremission therapy is essential. There is no consensus on a single 'best' postremission treatment, but it preferably includes intermediate or high-dose cytarabine-based chemotherapy, or SCT, depending on the risk group. Patients with good-risk AML should receive at least one cycle of intensive cytarabine-based consolidation chemotherapy. Patients with AML in the intermediate and poor-risk groups with an HLA-identical sibling might be candidates for allo-SCT, providing that their age and performance status allow for such treatment. According to clinical expert, allo-SCT can also be recommended for poor risk groups with an HLA-matched unrelated donor or alternative donors (cord blood, haploidentical donor).

Treatment pathways for the care of patients with AML largely follow current European guidelines published by the European Society for Medical Oncology (ESMO) and the ELN. Guidelines have also been published by the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation [49] and the National Comprehensive Cancer Network (NCCN) [23]. National guidelines are also available for Norway [24].

Figure 4.1 summarises the treatment pathway for patients with newly diagnosed AML across European countries (though deviations from it can be found) [26, 33, 50].

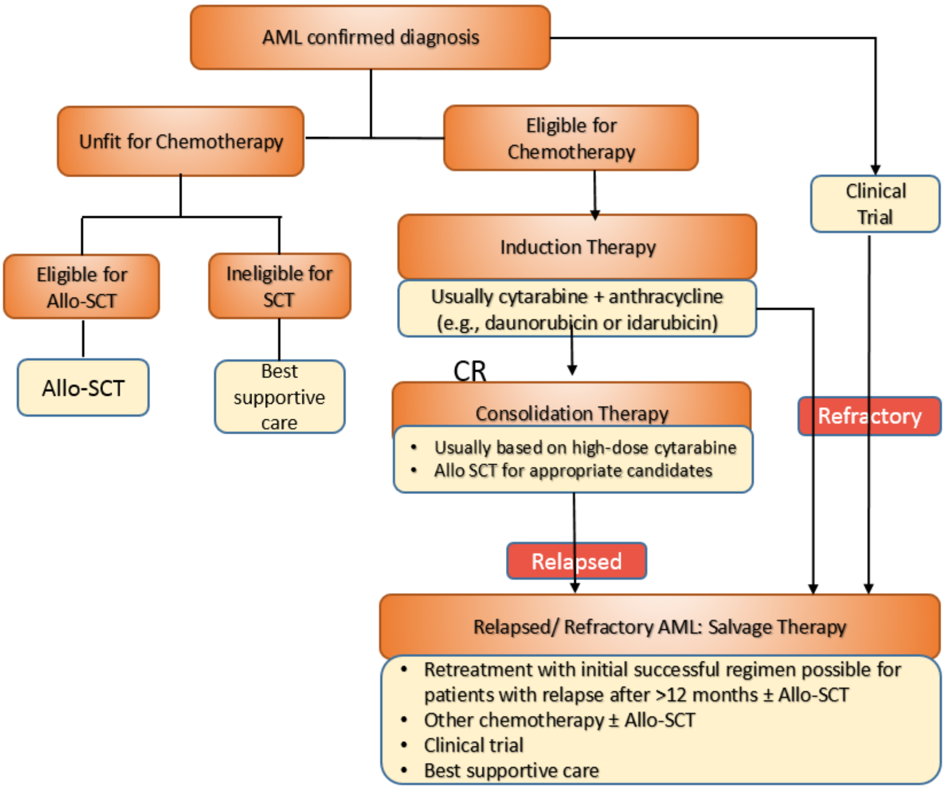


Figure 4.1. Treatment pathway for management of AML.

Target population

[A0007] What is the target population in this assessment?

This submission relates to patients found to have *de novo* AML only. The target population for midostaurin is adult patients with newly diagnosed AML who are FLT3 mutation positive and are suitable for intensive chemotherapy, as per the licence.

FLT3 mutation testing is required to identify patients for whom midostaurin is relevant. Currently, testing for FLT3-ITD is done in some patients for prognosis. The introduction of midostaurin will necessitate the introduction of routine testing for both FLT3-ITD and FLT3-TKD by a validated test in a timely manner in all patients eligible to receive intensive chemotherapy.

FLT3-ITD mutations are observed in 20%–25% of patients with *de novo* AML and in 30%–35% of patients with cytogenetically normal newly diagnosed AML (approximately 30% of all adult patients with AML). FTL3-TKD is observed in approximately 10% of cases. [23]

[A0023] How many people belong to the target population?

The estimated target population for midostaurin therapy is calculated based on the incidence of AML and the proportion of patients with FLT3 mutation-positive disease who are fit enough to receive standard chemotherapy.

The patient population in the pivotal study was restricted to patients younger than 60 years of age. This reflects the standard of care at the time that the pivotal study was initiated, i.e., at that stage, patients older than 60 years of age were deemed ineligible for standard induction and consolidation chemotherapy. Current practice is that all patients with AML who are fit, even if they are older than 60 years, should be treated with standard induction and consolidation chemotherapy; thus the target population includes adults over 18 years with no upper age limit.

The estimated incidence of AML is 3.4–3.7 per 100,000 for the EU overall. Approximately 60% of patients receive intensive chemotherapy according to a Swedish registry study [51]. FLT3 mutations are estimated to occur in approximately 30% of patients with AML [52, 53]. Given that the testing for FLT-3 mutation is not yet an established practice, there is no sufficient evidence to support an estimate proportion of patients for eligible for midostaurin treatment among all those diagnosed with *de novo* AML. The exact prevalence of FLT3 mutations across different age groups of patients with AML has not been established.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected effect of midostaurin on overall survival? This issue will cover the following outcomes: • OS • OS, censoring participants who receive SCT at the time of the transplant
D0006	What is the effect of midostaurin on disease progression, treatment response and relapse rate? This issue will cover the following outcomes: • Event-free survival (EFS) • Disease-free survival (DFS) • Complete response (CR) • Relapse rate
D0012	What is the effect of midostaurin on generic health-related quality of life?
D0013	What is the effect of midostaurin on disease-specific quality of life?

5.2 Results

Included studies

The assessment of clinical effectiveness was based on three studies: the RATIFY, IIT and UK NCRI AML17 trials. RATIFY was the placebo-controlled RCT most relevant to this assessment, and most of the results in this domain are based on the results of the RATIFY trial. The data summarised here are based on a data cut-off of 1st April 2015 (based an on interim report in April 2016).

The on-going single-arm phase II IIT trial provided supporting data on older patients. These data were mainly used in evaluating clinical effectiveness in an older population.

The UK NCRI AML17 trial compared chemotherapy with daunorubicin 60 mg/m^2 to high-dose daunorubicin used in induction. The results of the subgroup analysis of this study were applied only on the indirect comparisons related to OS. Key features of these studies are summarised below.

RATIFY trial

Detailed features of the RATIFY trial are provided in the MAH submission file and are summarised here.

RATIFY was a multicentre, phase III, randomised, double-blind, placebo-controlled trial assessing midostaurin in combination with standard chemotherapy followed by midostaurin monotherapy versus standard chemotherapy alone in patients with FLT3 mutation-positive AML. Patients were stratified by FLT3 mutation subtype (TKD vs. ITD high allelic mutation fraction [≥0.7] vs. ITD low mutation fraction [<0.7]) Table A2 in Appendix 1 provides further details of this study.

The study included patients with newly diagnosed FLT3 mutation-positive (FLT3-ITD or FLT3-TKD) AML aged ≥18 and <60 years. Patients with therapy-related AML, those with raised total bilirubin and/or with symptomatic congestive heart failure were excluded, as were patients who had received prior chemotherapy for myelodysplasia. The total number of patients was 717. Base-line characteristics of patients are shown in Table 5.1. Patient disposition is presented in Figure 5.2.

Table 5.1. Baseline characteristics of patients in the RATIFY trial

Characteristic	Midostaurin (n=360)	Placebo (n=357)	Total (n=717)
Age, years			
Mean (SD)	44.9 (10.4)	45.5 (10.8)	45.2 (10.6)
Median (range)	47.0 (19–59)	48.0 (18–60)	47.0 (18–60)
Male, n (%)	174 (48.3)	145 (40.6)	319 (44.5)

BSA, mean (SD) m^2	2.0 (0.29)	1.9 (0.28)	1.9 (0.28)
ECOG/Zubrod performance status, n (%)			
0	164 (45.6)	142 (39.8)	306 (42.7)
1	159 (44.2)	168 (47.1)	327 (45.6)
2	29 (8.1)	36 (10.1)	65 (9.1)
3	6 (1.7)	9 (2.5)	15 (2.1)
4	2 (0.6)	2 (0.6)	4 (0.6)
Region, n (%)			
North America	121 (33.6)	115 (32.2)	236 (32.9)
Non-North America	239 (66.4)	242 (67.8)	481 (67.1)
FLT3 mutation status, n (%)			
TKD	83 (23.1)	80 (22.4)	163 (22.7)
ITD (includes patients with both TKD and ITD)	276 (76.7)	274 (76.8)	550 (76.7)
ITD Allelic ratio <0.7	164 (45.6)	165 (46.2)	329 (45.9)
ITD Allelic ratio ≥0.7	112 (31.1)	109 (30.5)	221 (30.8)
No FLT3 gene mutation	1 (0.3)	3 (0.8)	4 (0.6)
Patients with prior MDS	14 (3.9)	16 (4.5)	30 (4.2)

Abbreviations: see List of abbreviations.

The trial comprised three treatment phases (Figure 5.1):

- Induction (1–2 cycles): cytarabine+daunorubicin+midostaurin OR placebo
- Consolidation (1–4 cycles): high-dose cytarabine+midostaurin OR placebo
- Maintenance (up to 12 cycles): midostaurin monotherapy OR placebo.

Receipt of SCT was not part of the RATIFY study protocol. Patients who received SCT did so according to the investigator's decision and, thus, this could occur in CR1 (i.e., first remission), after CR1 (i.e., after patients had relapsed following achieving their first remission) or for patients who were treatment failures after they stopped treatment during induction. SCT was considered the reason for treatment discontinuation only for SCTs performed for patients in CR1 and if the patient underwent SCT ≤2 months after discontinuing treatment. Patients undergoing SCT >2 months after stopping study treatment are likely to have been discontinued from the study for other reasons, and would have then progressed to SCT. Similarly, patients undergoing SCT after relapse or after treatment failure would have received other therapies (off study) to achieve CR before SCT.

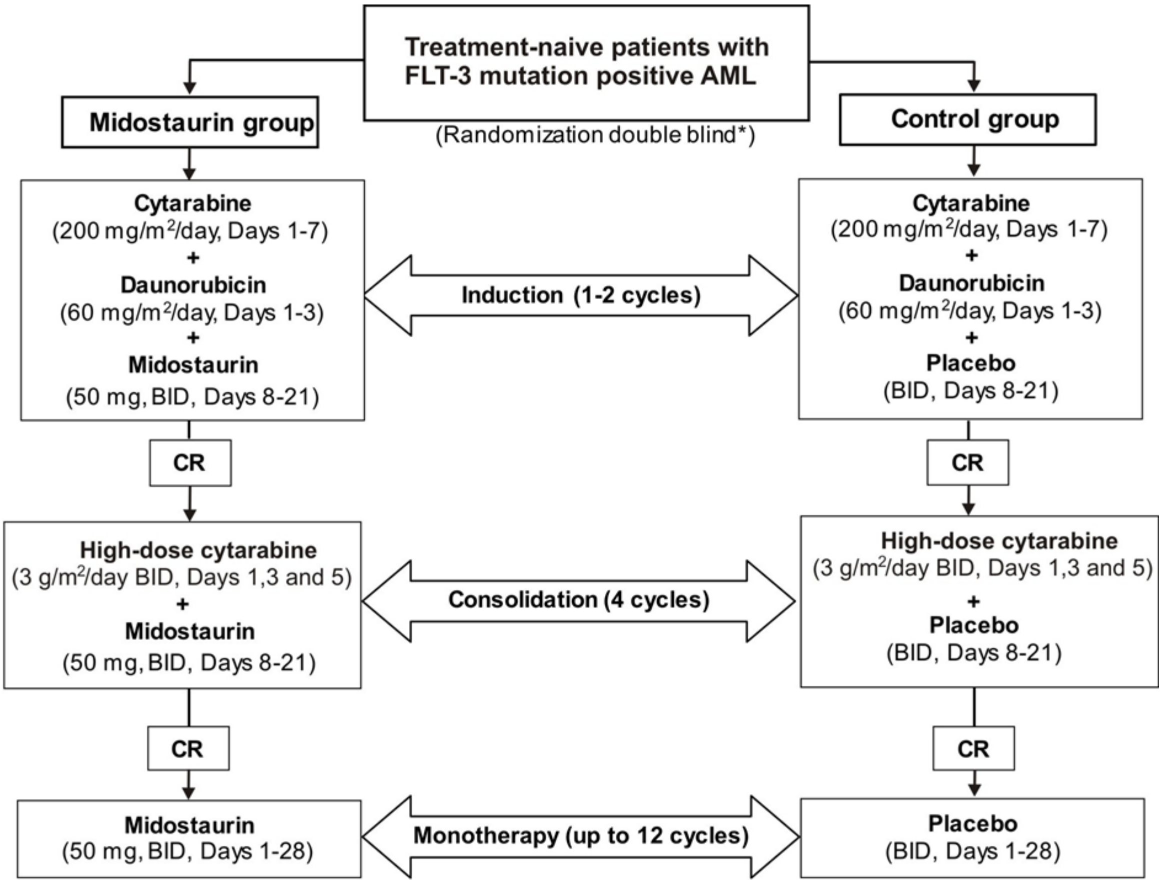


Figure 5.1. RATIFY trial study design.

Abbreviations: see List of abbreviations**. *Central randomisation within three strata: FLT3-TKD, FLT3-ITD with allelic ratio ≥0.7; FLT3-ITD with allelic ratio <0.7 [17].**

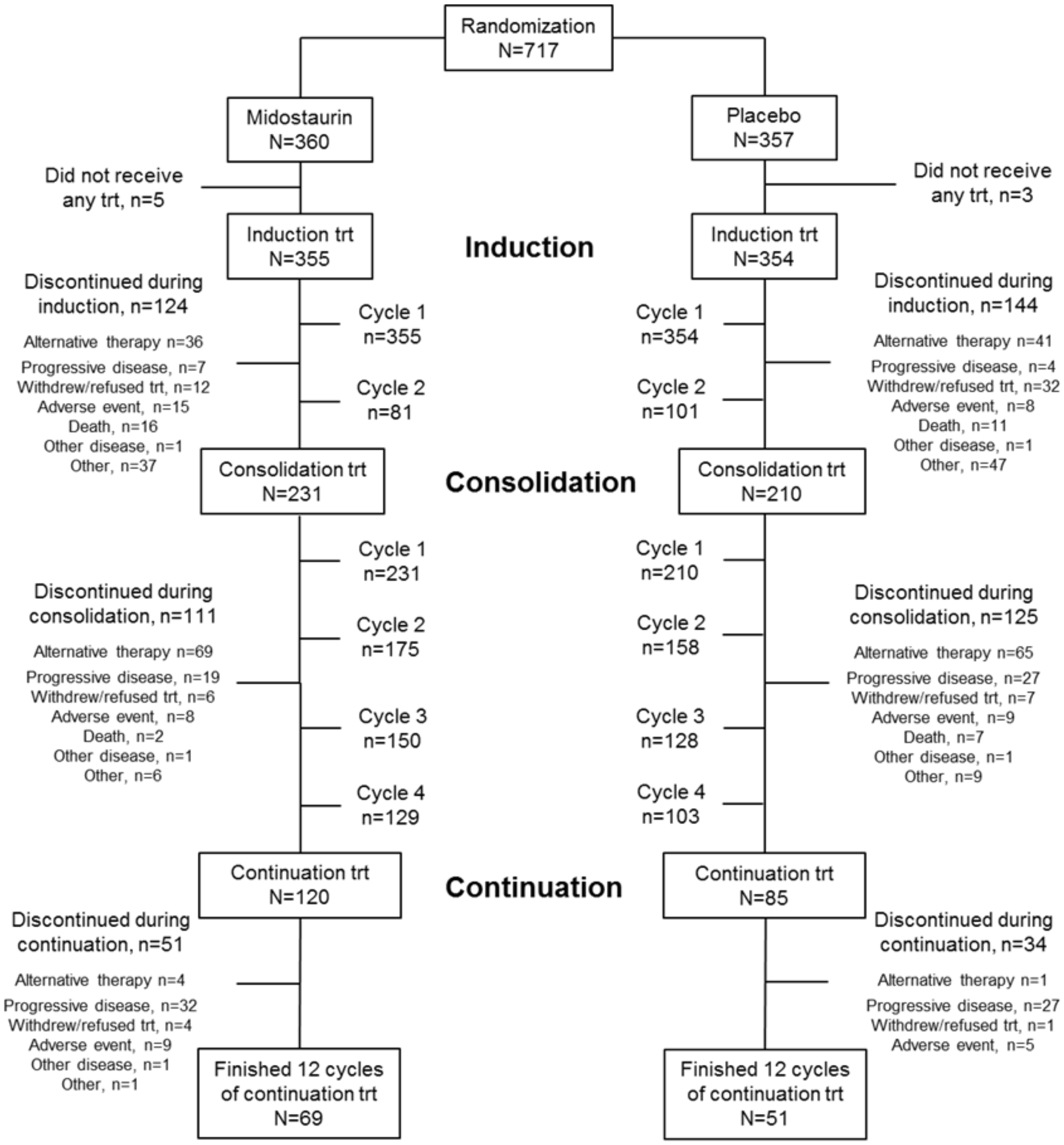


Figure 5.2. Patient disposition in the RATIFY trial.

Abbreviations: see List of abbreviations.

IIT trial (AMLSG 16-10)

The IIT in an on-going single-arm study evaluating the efficacy and safety of midostaurin added to chemotherapy (induction followed by consolidation) followed by midostaurin monotherapy in patients with newly diagnosed FLT3-ITD-positive AML. The primary objective was to compare outcomes for patients aged 18–60 years with those aged 61–70 years [17]. The total number of patients was 145 at the time of the interim CSR, with a data cut-off on 31-Dec-2015. Baseline characteristics of IIT trial are shown in Table 5.2.

Table 5.2. Baseline characteristics of patients in IIT trial

Demographic variables	All patients (n=145)	Patients ≤60 years (n=99)	Patients >60 years (n=46)
Age, years			
Mean (SD)	53 (11)	48 (9)	65 (3)
Median (range)	54 (20–69)	50 (20–60)	65 (61–69)
Sex, n (%)			
Men	61 (42)	38 (38)	23 (50)
Women	84 (58)	61 (62)	23 (50)
ECOG performance status, n (%)			
0	55 (38)	41 (42)	14 (30)
1	76 (53)	47 (48)	29 (63)
2	13 (9)	10 (10)	3 (7)
FLT3 mutation status, n (%)			
FLT3-TKD	3 (2)	2 (2)	1 (2)
FLT3-ITD ratio ≤0.50	69 (48)	47 (47)	22 (48)
FLT3-ITD ratio >0.50	76 (52)	52 (53)	24 (52)

Abbreviations: see List of abbreviations.

The primary endpoint was EFS after 2 years (defined as the time between study entry and any of the following: death during induction therapy, refractory disease or PR after response-adapted induction therapy, relapse and death in CR). RFS was defined as the time to relapse or death in CR for patients achieving a CR. Other endpoints included OS and CR rates.

Treatment comprised induction and consolidation followed by midostaurin monotherapy given for up to 1 year. Induction therapy comprised daunorubicin 60 mg/m² (days 1–3), cytarabine 200 mg/m² (continuously, days 1–7) and midostaurin 50 mg BID (from day 8 to 48 h before start of the next treatment cycle). The design of the study is characterised in Figure 5.3.

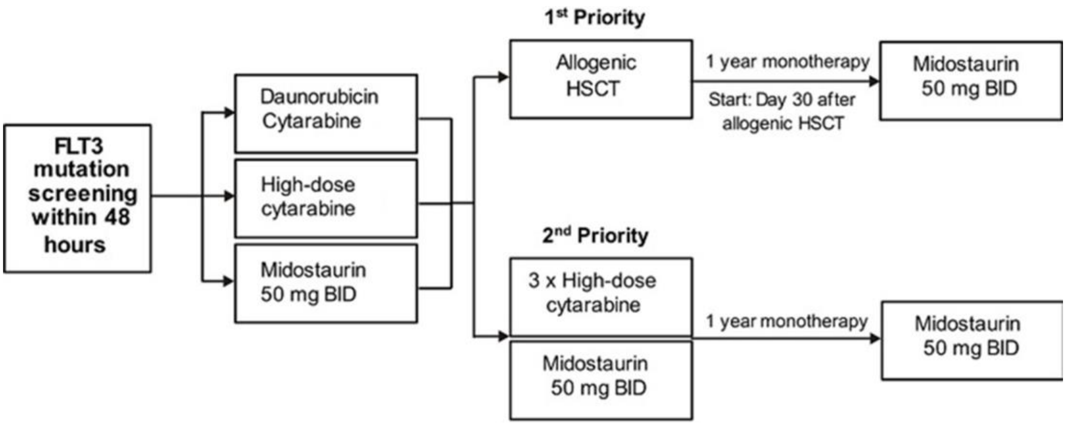


Figure 5.3. Study design of IIT AMLSG 16-10.

Abbreviations: see List of abbreviations.
Source: [17]

UK AML17, subgroup analysis of patients with FLT3-ITD mutated AML

In this study, 1206 patients were randomised in 1:1 to daunorubicin 90 mg/m² or 60 mg/m² in course 1, then 50 mg/m² in course 2 with cytarabine 100 mg/m² 12-h days 1–10 (course 1) and days 1–8 (course 2). The median age was 53 years (16–72); 54% were male; 84% had *de novo* AML, 10% secondary and 6% high-risk MDS; median presenting white blood cell count was 8.5(0.3–430)x10^9 cells/L; 10% had favourable cytogenetics, 72% intermediate and 18% adverse. [11]

Originally, the objectives of this study were to [10]:

1. Compare the overall efficacy of daunorubicin 90 mg/m^2 versus 60 mg/m^2 for induction in AML, based on findings of a RCT.
2. Compare the overall safety and toxicity of daunorubicin 90 mg/m^2 versus 60 mg/m^2 for induction in AML.
3. Compare daunorubicin 90 mg/m^2 versus 60 mg/m^2 for induction in AML in various subgroups.

In the overall study results, FLT3-ITD mutation status showed a significant interaction with treatment group in an explorative subgroup analysis. In this assessment, we considered subgroup analysis with patients with FLT3-ITD mutated AML (n=200), and performed an indirect comparison of midostaurin and daunorubicin 90 mg/m^2 in induction therapy based on subgroup analysis results concerning OS published in [11]. Only the results for OS were included in the indirect comparison, because the results from the other outcomes in this subgroup were not available. Furthermore, details of the baseline characteristics of sub-group of patients with FLT3-ITD mutated AML are not available for assessing the similarity of the patient groups compared in the indirect analysis. Baseline characteristics of the whole study population can be found in [10]. Despite these uncertainties, indirect comparison was performed, because high-dose daunorubicin was considered a relevant comparator to midostaurin. Further details of this study are provided in Appendix 1 and Table A3.

Mortality

[D0001] What is the expected effect of midostaurin on overall survival?

RATIFY trial

In the RATIFY trial, the risk of death was reduced by 23% during follow-up for midostaurin versus placebo (HR 0.77 [95% CI 0.63–0.95]; p=0.0078). The proportion of patients alive for midostaurin versus placebo at 1 and 5 years were [17]:

- 1 year – 76% (95% CI: 0.72–0.81) versus 68% (95% CI: 0.62–0.72), respectively
- 5 years – 51% (95% CI: 0.45–0.56) versus 43% (95% CI: 0.38–0.49), respectively.

During the RATIFY study, 57% of the patients received SCT, which exceeded the prestudy estimated rate of 15%. Overall SCT rates were 59.4% and 55.2% in the midostaurin and placebo groups, respectively, with approximately one-fifth of patients (22.2% and 19.3%, respectively) receiving SCT during the first CR. Similar to the OS results, results for OS censored at SCT showed a reduced risk of death for midostaurin over placebo (HR 0.75 [95% CI: 0.54–1.03]; p=0.0373). OS results and results for OS censored at SCT are summarised in Table 5.3 and in Figure 5.4 and Figure 5.5.

Table 5.3. Summary of OS results from the RATIFY trial

Endpoint	Midostaurin (n=360)	Placebo (n=357)	HR (95% CI), p value (one-sided)
Overall survival			
Median, months	74.7	25.6	HR 0.774 (0.629–0.953); p=0.0078
1 year, %	76	68	
3 year, %	54	47	
5 year, %	51	43	
Overall survival, censored at SCT			
Median, months	NE	NE	HR 0.749 (0.544–1.031); p=0.0373
1 year, %	82	70	
3 year, %	65	58	
5 year, %	64	56	

Abbreviations: see List of abbreviations.

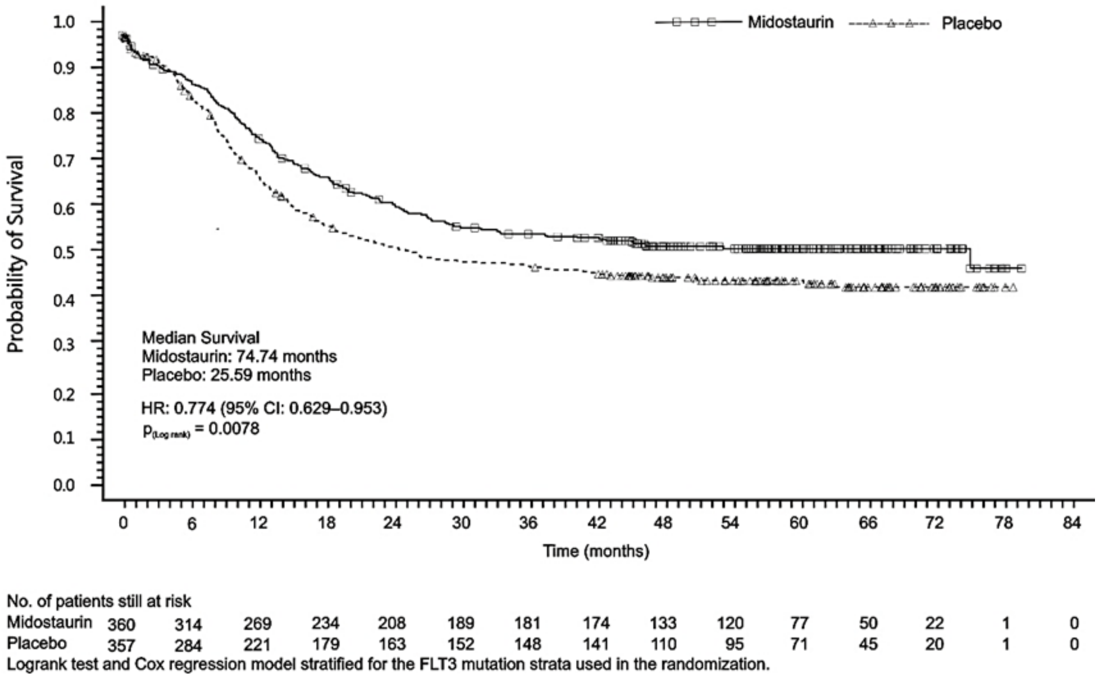
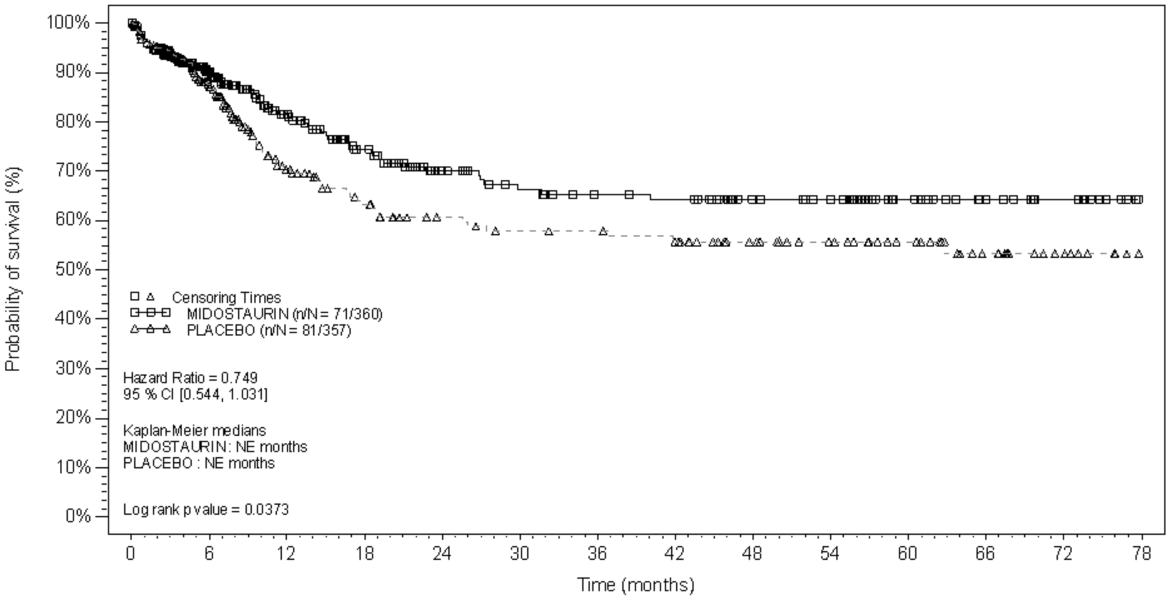


Figure 5.4. Overall survival, noncensored at the time of SCT.

Abbreviations: see List of abbreviations.
Source: [17]



No. of patients still at risk

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78
MIDOSTAURIN	360	192	136	106	80	70	64	62	49	44	27	17	10	0
PLACEBO	357	171	97	77	64	59	58	54	44	37	29	17	8	0

Figure 5.5. Kaplan–Meier curve for overall survival, censored at the time of SCT.

Abbreviations: see List of abbreviations.
Source: [17]

IIT trial

The following OS data were available for a median follow-up of 25.2 months (Table 5.4). The proportion of younger patients (≤60 years) alive at 2-year follow-up was 53.7%, whereas the proportion of older patients (>60 years) was 45.2%. The median survival rates were 28.5 months and 15.5 months, respectively.

Comparison of efficacy in the RATIFY and ITT studies was included in the MAH submission file as a confidential appendix. Similarly, comparison of efficacy of patients over 60 years of age from the ITT trial with historical controls was also provided as a confidential appendix. Consequently, further details of these results cannot be provided here.

Table 5.4. OS results for the IIT trial

Endpoint	All patients (n=145)	Aged ≤60 years (n=99)	Aged >60 years (n=46)
OS			
Median OS, months	24.7	28.5	15.5
2-year OS, %	51.0	53.7	45.2

Abbreviations: see List of abbreviations.

Indirect comparison of midostaurin and high-dose daunorubicin

Chemotherapy with high-dose daunorubicin (90 mg/m^2) used in induction was included as a comparator in this assessment, but direct evidence was not available. Comparison of midostaurin with standard induction and consolidation chemotherapy versus high-dose daunorubicin used in induction was performed indirectly using the Bucher method [54, 55]. Results are shown in Table 5.5. Indirect results comparing midostaurin with high-dose daunorubicin used in induction showed no difference between the treatments in terms of OS. Consequently, there is no evidence that midostaurin treatment would be more beneficial than high-dose daunorubicin used in induction, or vice versa. Several limitations apply to this indirect comparison, which are discussed in Section 8.

Table 5.5. Results of the indirect comparison of the RATIFY and UK NCRI AML17 trials

	Comparison	OS (95% CI)	Reference
RATIFY • **Full analysis set** • **n=717**	Midostaurin/DA 60 mg/m^2 vs. placebo/DA 60 mg/m^2	HR 0.774 (0.629–0.953)	[17]
UK NCRI AML17 • **subgroup of patients with FLT3-ITD mutation** • **n=200**	DA 90 mg/m^2 vs. 60 mg/m^2	HR 0.65 (0.43–0.96)	[11]
Indirect comparison • **Bucher method**	DA 90 mg/m^2 vs. midostaurin/DA 60 mg/m^2	HR 0.84 (0.54–1.31)	[18]

Abbreviations: see List of abbreviations. DA 60 mg/m^2=daunorubicin 60 mg/m^2 used in induction therapy; DA 90 mg/m^2=high-dose daunorubicin (90 mg/m^2) in induction therapy.

Subgroup analyses of OS

MAH presented prespecified subgroup analyses in the submission file (Figure 5.6). Subgroups assessed included breakdown by FLT3 randomisation/mutation/subtype, gender, region, race, prior MDS, WBC count and cytogenetics. The indication for midostaurin is for patients with newly diagnosed AML. Patients who had received prior treatment for MDS were not relevant to this assessment. A difference in OS was observed for men versus women.

A post-hoc subgroup analysis of data from RATIFY was performed regarding NPM1 status. Post data base lock, data regarding NPM1 status were available for 563 patients, 294 in the midostaurin group and 269 in the placebo group; of the midostaurin group, 55% had mutated NPM1 as did 60% of the placebo group. Furthermore, OS results in patients undergoing SCT and not undergoing SCT were included in the MAH submission. Results of these subgroup analyses are presented in

Table 5.6.

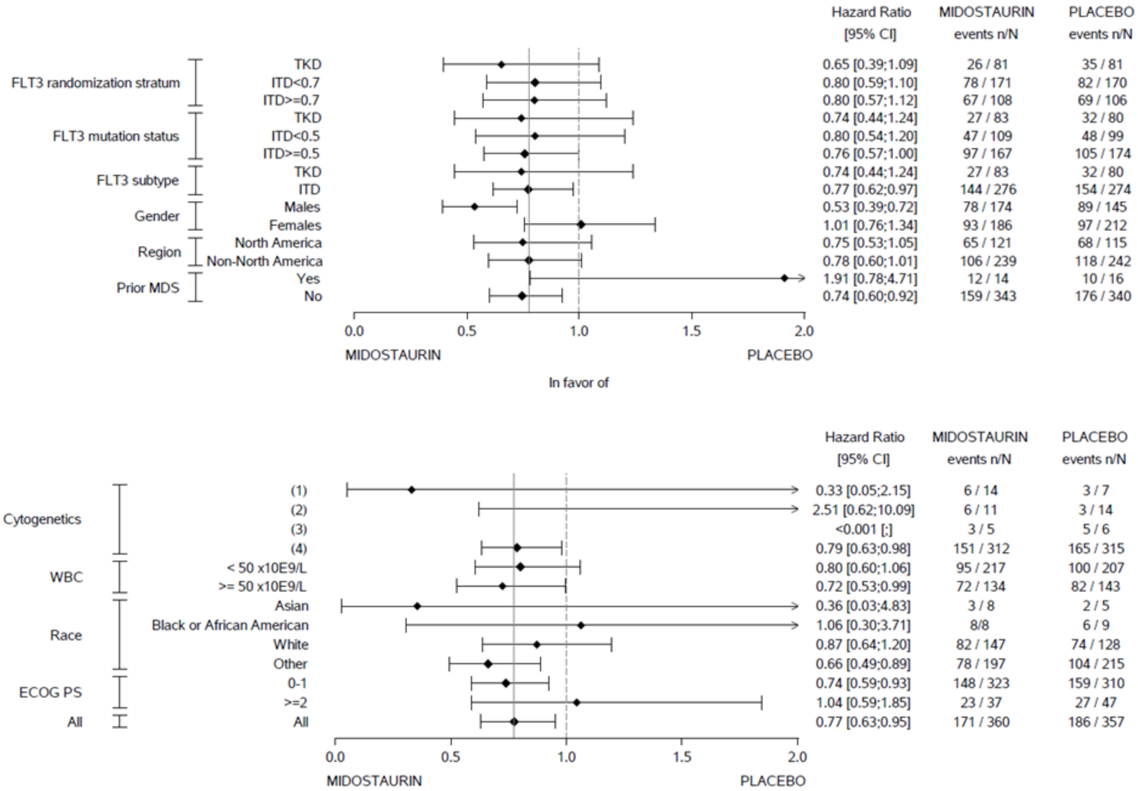


Figure 5.6. Prespecified subgroup analyses for OS.
Abbreviations: see List of abbreviations.
Source: [17].

Table 5.6. Results of the post-hoc subgroup analyses (RATIFY trial)

Endpoint	Midostaurin (n=360)	Placebo (n=357)	HR (95% CI), p value (one-sided)
Overall survival in patients undergoing SCT			
n	214	197	
Median, months	74.7	35.9	HR 0.780 (0.593–1.026); p=0.0376
1 year, %	84	77	
3 year, %	57	50	
5 year, %	52	45	
Overall survival in patients not undergoing SCT			
n	146	160	
Median, months	31.7	14.7	HR 0.798 (0.580–1.098); p=0.0822
1 year, %	66	54	
3 year, %	50	42	
5 year, %	49	41	
Overall survival in patients with NPM1 mutation			
n	NA	NA	
Median, months	NA	NA	HR 0.72 (0.52–1.01)
Overall survival in patients with NPM1 wild type			
n	NA	NA	
Median, months	NA	NA	HR 0.74 (0.54–1.03)

Abbreviations: see List of abbreviations.
Source: [17].

Morbidity

[D0006] What is the effect of midostaurin on disease progression, treatment response and relapse rate?

RATIFY trial

MAH presented the results for complete response rate, EFS, DFS and CIR of the RATIFY trial in the submission file. Results censored at SCT were also provided for EFS, DFS and CIR. Furthermore, DFS results were provided from first CR, censored from SCT, from the start of maintenance and censored at the end of maintenance, and from the end of maintenance. The results are summarised in Table 5.7 and in Figure 5.7 and Figure 5.8. Results for CRR (overall, %) are based on the alternative definition for CR rate and includes all CRs occurring during induction. Using the protocol-specified definition of a CR (a CR within 60 days of treatment initiation), the proportion of patients in the midostaurin arm achieving CR was 58.9% versus 53.5% for placebo (p=0.073).

Table 5.7. Summary of RATIFY trial results for complete response rate, event-free survival, disease-free survival and cumulative incidence of relapse

Endpoint	Midostaurin (n=360)	Placebo (n=357)	HR (95% CI), p value (one-sided)
Complete response rate, %			
Overall, %	65.0	58.0	p=0.027 (one-sided, CMH)
Induction: end of cycle 1	51.7	43.1	
Induction: end of cycle 2	13.3	14.8	
Event-free survival			
Median, months	10.2	5.6	HR 0.728 (0.613–0.866); p=0.0001
1 year, %	47	33	
3 year, %	32	23	
5 year, %	31	21	
Event-free survival, censored at SCT			
Median, months	10.1	5.6	HR 0.762 (0633–0.918); p=0.0019
1 year, %	46	31	
3 year, %	29	23	
5 year, %	28	21	
Disease-free survival from first CR			
Median, months	28.1	14.1	HR 0.663 (0.516–0.853); p=0.0006
1 year, %	70	54	
3 year, %	49	38	
5 year, %	48	36	
Disease-free survival from first CR, censored at SCT			
Median, months	20.7	14.5	HR 0.721 (0.536–0.970); p=0.0150
1 year, %	68	53	
3 year, %	44	39	
5 year, %	44	37	
Disease-free survival from start of maintenance and censored at end of maintenance			
n	115	79	
Median, months	NE	NE	HR 0.714 (0.430–1.184); p=0.0950
6 months, %	79	75	
10 months, %	72	67	
Disease-free survival from end of maintenance			
n	96	73	
Median, months	NE	NE	HR 1.369 (0.604–3.102); p=0.7753
1 year, %	77	91	
3 year, %	75	80	
5 year, %	75	72	
Cumulative incidence of relapse			
n	234	207	
Median, months	NE	17.6	HR 0.676 (0.515–0.888); p=0.0023
Cumulative incidence of relapse – censored at SCT			
Median, months	21.5	14.8	HR 0.761 (0.561–1.031); p=0.0387

Abbreviations: see List of abbreviations.
Source: [17]

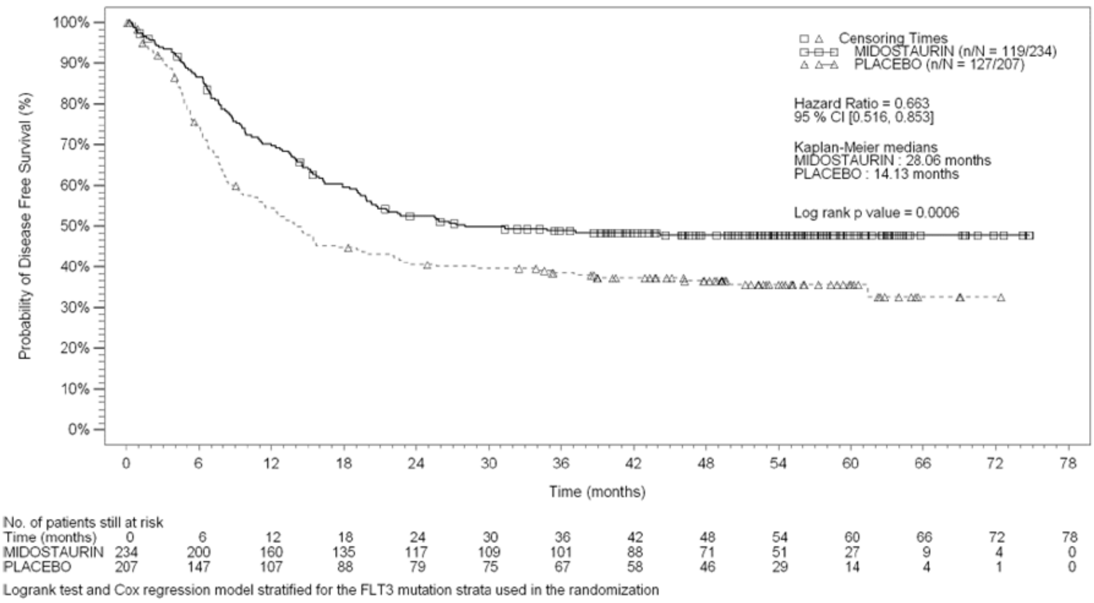


Figure 5.7. Disease-free survival, noncensored at the time of SCT.

Abbreviations: see List of abbreviations.
Source: [17]

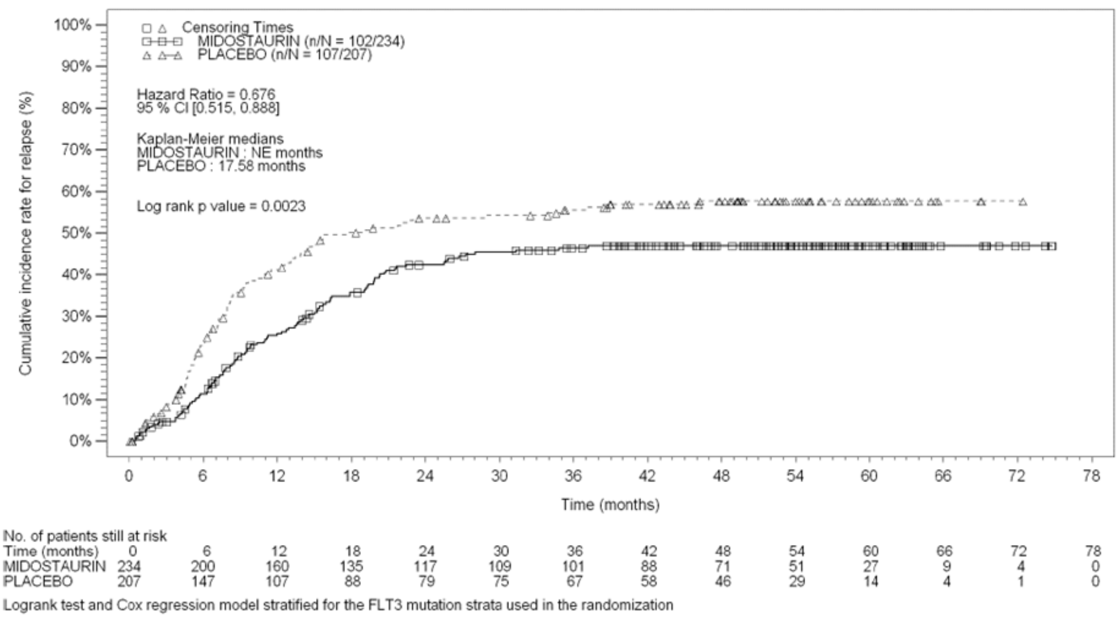


Figure 5.8. Cumulative incidence of relapse, noncensored at the time of SCT.

Abbreviations: see List of abbreviations.
Source: [17]

IIT trial

MAH presented results for complete response rate, EFS, RFS and CIR of the IIT trial in the submission file. Results were provided for the full population and separately for patients aged ≤60 and >60 years. The results were based on interim CSR, with a data cut-ff of 31-Dec-2015. The results are summarised in Table 5.8.

Table 5.8. Summary of single-arm IIT trial results for complete response, event-free survival, relapse-free survival and cumulative incidence of relapse

Endpoint	All patients (n=145)	Aged ≤60 years (n=99)	Aged >60 years (n=46)
CR, n (%)	107 (74)	76 (77)	31 (67)
EFS			
Median EFS, months	10.7	13.8	9.3
2-year EFS, %	34.6	38.2	27.1
RFS			
Median RFS, months	21.2	25.9	18.7
2-year RFS, %	46.7	51.3	36.6
Cumulative incidence of relapse, %	27.8	22.2	40.0

Abbreviations: see List of abbreviations.
Source: [17]

An exploratory analysis comparing IIT trial data with historical controls was provided in the MAH submission file. Kaplan–Meier curves for RFS in patients treated with midostaurin and with historical controls aged 18–60 and 60–70 years are shown in Figure 5.9.

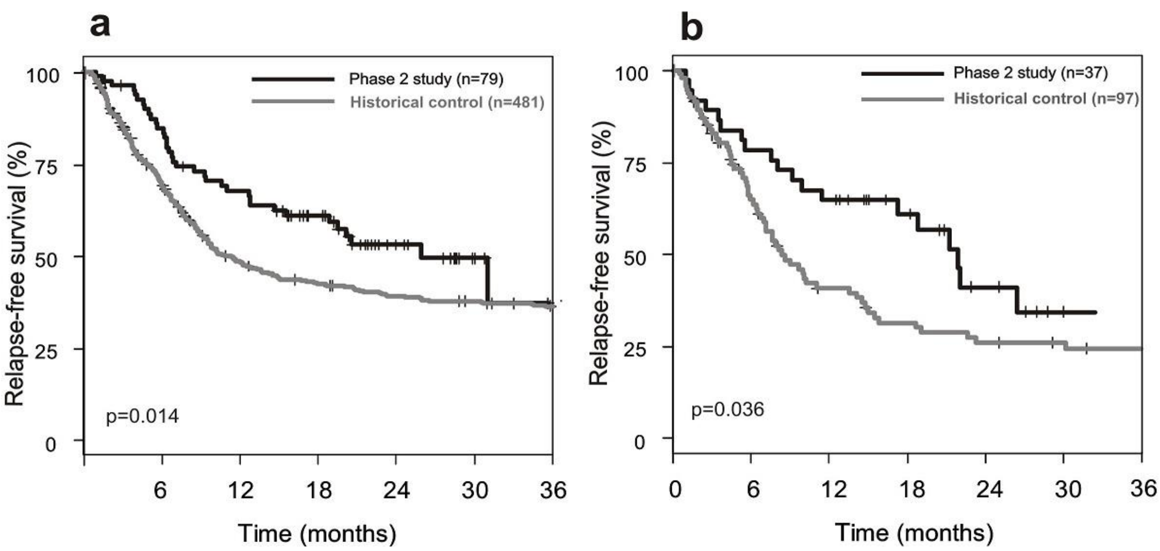


Figure 5.9. RFS in patients treated with midostaurin in the IIT and historical controls: a) patients aged 18–60 years; b) >60–70 years.

Abbreviations: see List of abbreviations.
Source: [17]

Health-related quality of life

[D0012] What is the effect of midostaurin on generic health-related quality of life?

There are no results available on the effect of midostaurin on the generic HrQoL, because this has not been investigated in the studies completed to date.

[D0013] What is the effect of midostaurin on disease-specific quality of life?

There are no results available on the effect of midostaurin on the disease-specific quality of life, because this has not been investigated in the studies completed to date.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is midostaurin in relation to the comparators? The following outcomes will be covered in this issue: • AEs (adverse events) • serious AEs (SAE) • discontinuation because of AE • death as SAE • AEs of special interest • grade ≥3 AEs Dose and time dependencies of harms and patient groups that are most likely to be harmed will be covered under this issue.

6.2 Results

Included studies

This section is based on RATIFY and IIT trial results. Please see above (EFF domain) for details. The data were extracted from the MAH submission file [17] and the update as per PKC412A2301 CSR Amendment 1 provided by MAH at later stage.

Patient safety

[C0008] How safe is midostaurin in relation to the comparators?

RATIFY trial

<u>Adverse events</u>

A summary of the AEs recorded in the RATIFY study is provided in Table 6.1 according to the MAH submission. There were 36 deaths on-treatment (i.e., within 30 days of the last treatment; 15 and 21 in the midostaurin and placebo arms, respectively). Approximately 50% of the patients in both groups experienced a grade 3-4 SAE and approximately 75% of patients in both groups reported at least one grade 3–4 AE considered to be related to treatment. Of the patients, 6.7% in the midostaurin group and 5.1% in the placebo discontinued therapy because of grade 3–4 AEs.

Haematological AEs were the most frequently reported AEs in both treatment groups, with ≥89% of patients in both groups reporting grade 3–4 thrombocytopaenia, anaemia and neutropaenia (Table 6.1). The most frequent nonhaematological grade 3–4 AEs in the midostaurin group were device-related infections (15.7%), diarrhoea (15.4%) and exfoliative dermatitis (13.6%), and in the placebo arm were hypokalaemia (17.0%), diarrhoea (15.2%) and pneumonia (14.0%). In addition to the AEs listed in Table 6.1, QTc prolongation has been observed in patients receiving midostaurin.

Table 6.1. Summary of AEs in RATIFY, including grade 3–4 AEs reported in ≥10% of patients receiving midostaurin regardless of relationship to study drug: overall and during maintenance therapy

System organ class AEs	Overall		Maintenance therapy only	
	Midostaurin (n=345)	Placebo (n=335)	Midostaurin (n=120)	Placebo (n=85)
Death, n (%)	15 (4.3)	21 (6.3)	0	1 (1.2)
Grade 3–4 SAEs, n (%)	169 (49.0)	164 (49.0)	16 (13.3)	10 (11.8)
Grade 3–4 AEs, n (%)	344 (99.7)	335 (100.0)	49 (40.8)	40 (47.1)
Grade 3–4 AEs suspected to be related to treatment, n (%)	269 (78.0)	252 (75.2)	NR	NR
Withdrawal because of grade 3–4 AEs, n (%)	23 (6.7)	17 (5.1)	4(3.3)	4(4.7)
Grade 3–4 AEs reported in ≥10% of patients receiving midostaurin, n (%)				
Thrombocytopaenia	337 (97.7)	326 (97.3)	3 (2.5)	13 (15.3)
Neutropaenia	329 (95.4)	327 (97.6)	10 (8.3)	8 (9.4)
Anaemia	322 (93.3)	298 (89.0)	1 (0.8)	0
Febrile neutropaenia	288 (83.5)	278 (83.0)	1 (0.8)	0
Leucopaenia	93 (27.0)	101 (30.1)	3 (2.5)	0
Lymphopaenia	69 (20.0)	76 (22.7)	8 (6.7)	2 (2.4)
Device-related infection	54 (15.7)	33 (9.9)	0	0
Diarrhoea	53 (15.4)	51 (15.2)	1 (0.8)	2 (2.4)
Hypokalaemia	48 (13.9)	57 (17.0)	0	1 (1.2)
Dermatitis exfoliative	47 (13.6)	25 (7.5)	1 (0.8)	0
Pneumonia	45 (13.0)	47 (14.0)	0	0
Increased ALT	45 (13.0)	32 (9.6)	5 (4.2)	4 (4.7)

Abbreviations: see List of abbreviations.
Source: [17]

Serious AEs

Almost half of the patients (49% and 49% of patients in the midostaurin and placebo arms, respectively) experienced at least one grade 3-4 SAE and over half of these were suspected to be related to study treatment (Table 6.2). Febrile neutropaenia, decreased neutrophil count, decreased platelet count, device-related infection and pneumonia were the most frequently occurring SAEs in the midostaurin group, each with incidences >5%. Of those patients receiving midostaurin maintenance monotherapy, 12% experienced a SAE (compared with 11% for placebo).

Table 6.2. Grade 3-4 SAEs reported in ≥ 2% of patients in the midostaurin group regardless of relationship to midostaurin or placebo in the RATIFY trial

SAE, n (%)	Overall		Maintenance therapy only	
	Midostaurin (n=345)	Placebo (n=335)	Midostaurin (n=120)	Placebo (n=85)
Any event	169 (49.0)	164 (49.0)	16 (13.3)	10 (10.8)
Febrile neutropaenia	53 (15.4)	53 (15.8)		
Neutrophil count decreased	29 (8.4)	33 (9.9)	3 (2.5)	1 (1.2)
Device-related infection	23 (6.7)	12 (3.6)	—	—
Platelet count decreased	23 (6.7)	28 (8.4)	0	2 (2.4)
Pneumonia	23 (6.7)	23 (6.9)	0	0
Sepsis	16 (4.6)	14 (4.2)	—	—
Haemoglobin decreased	12 (3.5)	9 (2.7)	0	0
Hypotension	12 (3.5)	1 (0.3)	0	0
Neutropenic infection	12 (3.5)	6 (1.8)	—	—
Pneumonitis	11 (3.2)	8 (2.4)	—	1 (1.2)
Dermatitis exfoliative	10 (2.9)	1 (0.3)	—	—
Neutropaenic sepsis	10 (2.9)	1 (0.3)	—	—
AST increased	9 (2.6)	1 (0.3)	1 (0.8)	0
ALT increased	8 (2.3)	3 (0.9)	0	0
Hypokalaemia	8 (2.3)	3 (0.9)	—	—
Infection	8 (2.3)	3 (0.9)	1 (0.8)	0
Leucopoenia	8 (2.3)	7 (2.1)	1 (0.8)	0
Renal failure	8 (2.3)	2 (0.6)	—	—
Acute respiratory distress syndrome	7 (2.0)	3 (0.9)	—	—
Colitis	7 (2.0)	9 (2.7)	0	0
Hypoxia	7 (2.0)	0	—	—

Abbreviations: see List of abbreviations.
Source: [17]

<u>Discontinuation because of AEs</u>

Overall, 23(6.7%) patients in the midostaurin group and 17 (5.1%) patients in the placebo group discontinued therapy because of grade 3–4 AEs (Table 6.3). The events leading to discontinuation in more than one patient were dermatitis exfoliative, increased ALT, increased AST, decreased neutrophil count, and renal failure in the midostaurin group and febrile neutropaenia, decreased neutrophil count and decrease platelet count in the placebo group. In both treatment groups, four patients discontinued treatment because of AEs during the maintenance therapy.

Table 6.3. Grade 3–4 AEs leading to treatment discontinuation in RATIFY in at least 1 patients in the midostaurin group

Grade 3–4 AEs leading to discontinuation, n (%)	Midostaurin (n=345)	Placebo (n=335)
Overall incidence	23 (6.7)	17 (5.1)
Dermatitis exfoliative	4 (1.2)	0
ALT increased	3 (0.9)	1 (0.3)
AST increased	2 (0.6)	0
Neutrophil count decreased	2 (0.6)	2 (0.6)
Renal failure	2 (0.6)	0
Atrioventricular block	1 (0.3)	0
Central nervous system leukaemia	1 (0.3)	0
Cervical vertebral fracture	1 (0.3)	0
Chloroma	1 (0.3)	0
Device-related infection	1 (0.3)	0
Febrile neutropaenia	1 (0.3)	3 (0.9)
Haemoglobin decreased	1 (0.3)	0
Hypercholesterolaemia	1 (0.3)	0
Hypertriglyceridaemia	1 (0.3)	0
Jaundice	1 (0.3)	0
Jaw fracture	1 (0.3)	0
Myocardial ischaemia	1 (0.3)	0
Platelet count decreased	1 (0.3)	4 (1.2)
Pneumonitis	1 (0.3)	1 (0.3)
Pregnancy	1 (0.3)	0
Pulmonary haemorrhage	1 (0.3)	0
Rib fracture	1 (0.3)	0
Staphylococcal infection	1 (0.3)	0
Troponin T increased	1 (0.3)	1 (0.3)

Abbreviations: see List of abbreviations.
Source: [17]

Death as SAE

According to MAH submission, on-treatment deaths (those occurring within 30 days of last dose of study drug) occurred in 15 (4.3%) and 21 (6.3%) patients in the midostaurin and placebo arms, respectively. Three deaths resulted from AML/disease progression (one for midostaurin and two for placebo) and most deaths resulted from infections.

Most deaths occurred during the induction phase (14 [4.1%] patients in the midostaurin group and 11 [3.3%] patients in the placebo group). Nine and seven deaths (2.6% and 2.1%) in the midostaurin and placebo groups, respectively, were suspected to be related to the study medication. Causes in the midostaurin group included sepsis in two patients, and multiorgan failure, infectious colitis, acute respiratory failure, colitis, myocardial infarction, neutropaenic sepsis, pulmonary haemorrhage and septic shock in one patient each.

IIT trial

The safety data presented here are fully based on the MAH submission [17], in which data from the IIT trial were reported for the initial analysis, which included 145 patients with a median follow-up of 25.2 months and a comparison of the safety profile of midostaurin in patients ≤60 years and 61–70-years old. AEs, AEs of grade 3–4 and treatment-related AEs are summarised in Table 6.4 for the all the patients and separately for patients aged 18–60 and over 60 years. Furthermore, a summary of treatment-related serious AEs and any AEs leading to treatment discontinuation in more than 1 patient is provided in Table 6.5.

Table 6.4. Summary of the incidence of AEs and incidence of grade ≥3 treatment-related AEs occurring in ≥5% of patients in the IIT

Endpoint	All patients (n=144)	Aged ≤60 years (n=98)	Aged >60 years (n=46)
Any AE	144 (100)	98 (100)	46 (100)
Deaths (during study treatment and 30-day follow-up period)	16 (11)	6 (6)	10 (22)
Other serious AEs	94 (65)	61 (62)	33 (72)
Withdrawn from Rydapt® treatment because of AEs	41 (28)	26 (27)	15 (33)
Treatment-related AEs	135 (94)	93 (95)	42 (91)
Nonhaematological treatment-related grade ≥3 AEs reported in ≥5% of patients overall or in either age group, n (%)			
Nausea	17 (12)	8 (8)	9 (20)
Lung infection	14 (10)	7 (7)	7 (15)
QT prolongation	10 (7)	4 (4)	6 (13)
Sepsis	10 (7)	5 (5)	5 (11)
Device-related infection	8 (6)	6 (6)	2 (4)
Diarrhoea	9 (6)	5 (5)	4 (9)
Vomiting	7 (5)	5 (5)	2 (4)
Hypokalaemia	7 (5)	5 (5)	2 (4)
Gastrointestinal inflammation	7 (5)	6 (6)	1 (2)
ALT elevation	7 (5)	5 (5)	2 (4)
Hepatobiliary disorder	5 (3)	5 (5)	0
Hypertension	4 (3)	1 (1)	3 (7)
Haematological treatment-related grade ≥3 AEs reported in ≥5% of patients, n (%)			
Decreased platelet count	80 (56)	55 (56)	25 (54)
Decreased haemoglobin	66 (46)	42 (43)	24 (52)
Leucopoenia	71 (49)	48 (49)	23 (50)
Neutropaenia	44 (31)	32 (33)	12 (26)
Febrile neutropaenia	34 (24)	22 (22)	12 (26)

Abbreviations: see List of abbreviations.
Source: [17]

Table 6.5. Summary of treatment-related SAEs in ≥3% of patients and AEs leading to treatment discontinuation in at least 1 patient in the IIT

Endpoint	All patients (n=144)	Aged ≤60 years (n=98)	Aged >60 years (n=46)
Treatment-related SAEs in ≥3% of patients overall, n (%)			
Lung infection	7 (5)	2 (2)	5 (11)
Platelet count decreased	7 (5)	4 (4)	3 (7)
Electrocardiogram QT prolonged	6 (4)	4 (4)	2 (4)
Diarrhoea	5 (3)	5 (5)	0
Sepsis	5 (3)	3 (3)	2 (4)
Cardiac disorder	4 (3)	4 (4)	0
Colitis	4 (3)	4 (4)	0
Nausea	4 (3)	2 (2)	2 (4)
Vomiting	4 (3)	3 (3)	1 (2)
Hepatobiliary disease	4 (3)	4 (4)	0
Alanine aminotransferase	3 (2)	1 (1)	2 (4)
AEs leading to treatment discontinuation in ≥2 patients overall, n (%)			
Graft vs. host disease	5 (3)	1 (1)	4 (9)
Nausea	3 (2)	2 (2)	1 (2)
Platelet count decreased	3 (2)	3 (3)	0
Cardiac disorders	2 (1)	2 (2)	0
Electrocardiogram QT prolonged	2 (1)	0	2 (4)
Hepatobiliary disease	2 (1)	2 (2)	0

Abbreviations: see List of abbreviations. **Source:** [17]

7 PATIENT INVOLVEMENT

After consultation with patient organisations, a Romanian patient with AML was identified. An open interview, based on the HTAi questionnaire template, was conducted with this patient. The experiences of the patient informed to some extend the outcomes taken into consideration for this joint assessment. The process for patient involvement in joint assessment REA is still under development.

8 DISCUSSION

Description and technical characteristics of midostaurin

Midostaurin is a new orally administrated multi-target receptor tyrosine kinase inhibitor acting against FLT3, KIT, KDR, PKC, and PDGFR, leading to cell cycle arrest and apoptosis. It is a staurosporine analog with potent activity against both ITD- and TKD-mutant as well as against wild-type FLT3. [B0001]

Health problem and current use of midostaurin

AML is a rare condition, having an estimated incidence of 3.7 per 100,000 for the EU overall and is largely diagnosed in older patients. Approximately one-third of patients have FLT3 mutation-positive disease. [A0023].

Overall, the 5-year survival rate for AML is 20%–30%. Younger patients have better outcomes compared with older patients. Patients with FLT3 mutation have worse outcomes for OS, time to relapse and DFS compared with patients without FLT3. [A0007]

Midostaurin received marketing authorisation (EC decision) on 18th September 2017 for AML indication: in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single-agent maintenance therapy for adults with newly diagnosed AML who are FLT3 mutation positive. The current use of midostaurin for AML treatment so far has been limited to clinical trials.

The wide variation in standard chemotherapy across Europe could affect the applicability of results from the RATIFY study. The most-common therapies for AML comprise induction therapy with a combination of an anthracycline and continuous infusion of cytarabine followed by SCT, depending on risk group. Several anthracyclines at different dosages are recommended for use across European countries (e.g., idarubicin). Mitoxantrone can also be used instead of daunorubicin.

SCT is widely used in AML after induction therapy. Exclusion of SCT from the PICO in the scope of this assessment was justified by the RATIFY trial design, which permitted the use of SCT (allogeneic or autologous), although patients who underwent SCT were not to resume midostaurin/placebo therapy following SCT. Previous midostaurin treatment would not prevent eligible patients from SCT. Consequently, midostaurin and SCT treatments are not mutually exclusive and there is no available evidence to support such a comparison.

GO was considered by the MAH as a relevant comparator because it has been used in France in a compassionate-use program since 2014 [1]. GO is currently under evaluation at EMA and did not have a license at the time of this assessment. Thus, GO was not considered in this European assessment as a relevant comparator because of its limited use in a selected population in only one member state.

Clinical effectiveness

Overall survival

Midostaurin in combination with standard induction and consolidation chemotherapy improved OS in patients aged 18–60 years who are fit for chemotherapy (HR= 0.77, 95%CI: 0.63–0.95, p=0.0078). Thus, the risk of death was reduced by 23% during follow-up for midostaurin versus placebo. The proportion of patients alive was significantly higher at both the 1- and 5-year follow-ups, demonstrating both short- and long-term positive effects of midostaurin on survival. Median OS was 25.6 months (95% CI: 18.6–42.9) for placebo and 74.7 months (95% CI: 31.5–not estimable) for midostaurin-based therapy. The large difference in the OS medians is at least partly explained by the plateau effect and very few deaths occurred after 3 years of therapy, irrespective of the treatment group. Given this evident plateau effect, the absolute OS gain cannot be reliably determined. We, as authors, do not consider interpreting 49 months' difference in OS medians as a reliable estimate for OS gain. Patients over 60 years of age have been studied in a single single-arm trial, but RCT-based evidence of the benefits of midostaurin in terms of OS among older patients is currently lacking. [D0001]

Similar to the OS results, results for OS censored at SCT show a reduced risk of death for midostaurin over placebo (HR 0.75 [95% CI: 0.54–1.03]; p=0.0373). Approximately the same relative risk reduction in OS was demonstrated among patients undergoing SCT, patients not undergoing SCT and the overall study population. Consequently, SCT is unlikely to significantly confound the effect of midostaurin on OS, despite the high rates of patients receiving SCT (59.4% and 55.2% in the midostaurin and placebo groups, respectively). [D0001]

There was no relevant heterogeneity in the effect on OS observed in subgroup analyses, except a difference in effect between males and females. This difference was not seen in subgroup analyses of EFS or other secondary efficacy endpoints. The effect was also consistent for OS and EFS censored for SCT between males and females. In conclusion, the overall evidence does not allow us to conclude that the effect of midostaurin would be dramatically different between males and females.

The MAH provided post-hoc subgroup analysis regarding NPM1 status. In terms of OS, relative risk reduction was approximately the same irrespective of NPM1 mutation status. These results were adjusted for the FLT3 mutation factor. It is unknown if the interaction of NPM1 and FLT3 modifies the overall effect of midostaurin. These analyses were requested from the MAH during the assessment, but MAH could not provide them within the timeframe available. It remains therefore unclear whether the efficacy of midostaurin for, e.g., patients with NPM1 wild type and FLT3 ITD with an allelic ratio ≥0.7 or patients with a NPM1 mutation and a FLT3 ITD mutation with allelic ratio <0.7, would be the same.

Indirect comparison of midostaurin in combination with standard induction and consolidation chemotherapy versus induction and consolidation chemotherapy with high-dose daunorubicin (90 mg/m^2) used during induction showed no difference between the treatments in terms of OS (daunorubicin 90 mg/m^2 versus midostaurin/daunorubicin 60 mg/m^2, HR=0.84, 95% CI: 0.54–1.31). Consequently, there is no evidence that midostaurin treatment would be more beneficial than high-dose daunorubicin used during induction, or vice versa. Indirect comparisons were conducted by authors.

Serious limitations apply to these comparisons. First, the indirectness of evidence reduces the quality and credibility of the result overall. Second, full details of the FLT3-mutated subpopulation were not available for the study comparing 90 mg/m^2 and 60 mg/m^2 daunorubicin and thus, does not allow for the assessment of the similarity of the patient groups compared indirectly. Third, estimates of the effect of daunorubicin 90 mg/m^2 were based on a post-hoc subgroup analysis, which might have impact on the result compared with an analysis conducted directly as a primary analysis for the full analysis set. Fourth, follow-up times for OS differed between the UK NCRI AML17 and RATIFY trials, being only 3 years in the former and approximately 6 years in the latter. This might have impact on the result if it is expected that the OS effect is time dependent. Fifth, there is limited similarity in the common reference arms (variation in regimens). The exact implications of these limitations are not fully clear because of the lack of information available. Consequently, drawing conclusions from this indirect comparison should be cautioned.

Overall, evidence for the OS effect of midostaurin with standard chemotherapy versus standard chemotherapy is based on one appropriately designed and analysed RCT with a low risk of bias (see Appendix 1 and Tables A4 and A5). However, because of the design of the RATIFY trial, the disposition of patients and complex treatment overall, the effects of midostaurin during continuation therapy are difficult to assess reliably, and only a small proportion of patients received midostaurin as a continuation therapy.

The direct evidence is of high quality (see Appendix 1 and Tffigable A6). However, the indirect comparison of midostaurin and high-dose daunorubicin used during induction has several limitations and the overall quality of indirect evidence is low.

There are limitations in applicability related to evidence for OS. RCT evidence was only available for patients aged 18–60 years. The average age of patients in the RATIFY trial was 45.2 years, which is likely to be less than the average age of those typically treated in clinical practice. Also, the proportion of patients undergoing SCT in the RATIFY trial is likely to be higher than for those treated in clinical practice. This might be a reflection of the younger and healthier patient population used in the trial.

There was only very limited evidence for patients aged over 60 years and this evidence was based on a single-arm trial. Given these results, there is no reason to suspect that patients aged 60 years or more would not benefit from midostaurin. Furthermore, the suitability of a patient for chemotherapy is more critical in terms of eligibility for treatment than is their actual age. However, there is a clear evidence gap concerning the effects of midostaurin in the older AML population. Significant proportion of the patients treated in clinical practice are older than 60 years of age, and the result of treatment can be generally expected to be worse than for younger patients.

Another issue related to the applicability is the variation in the standard induction and consolidation chemotherapy across countries and regions. Midostaurin has been studied in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and with patients in DR followed by midostaurin monotherapy. There is no evidence of midostaurin in combination with other induction and consolidation alternatives, except for those used in RATIFY.

Other outcomes (EFS, CR, DFS, and CIR)

EFS was improved by 27% in the midostaurin group compared with standard induction and consolidation chemotherapy (HR=0.73, 95% CI: 0.61–0.87, p=0.0001). EFS was a key secondary endpoint to be tested in a hierarchical manner if the OS endpoint was significant. EFS results censored at SCT were consistent with this result (HR=0.76, 95% CI: 0.63–0.92, p=0.0019). The effect of midostaurin on EFS was homogeneous across the subgroups, and the heterogeneity of effect between males and females that was seen in the OS result was not observed. In the IIT trial, median EFS was 13.8 months in patients aged ≤60 years. In patients over 60 years, the median EFS was 9.3 months. This indicates longer EFS for younger patients.

Similarly, DFS from first CR was improved by 34% (HR= 0.66, 95% CI: 0.52–0.85, p=0.0006) and DFS censored at SCT improved by 28% (HR=0.72, 95% CI: 0.54–0.97, p=0.0150) in the midostaurin group compared with standard induction and consolidation chemotherapy. In addition, the results regarding DFS were in line with the OS results.

Overall, the CR rate was higher in the midostaurin group (65% vs. 58%, p=0.027, one sided). In the IIT trial, a slightly higher proportion of patients in CR was observed in patients ≤60 years than in patients over 60 years (77% vs. 67%).

Comparison of the CIR between the two treatment groups showed that midostaurin reduced the risk of relapse (HR 0.676 [95% CI: 0.52–0.89]; p=0.0023). Censoring for SCT reduced the difference between the treatment groups.

Overall, key secondary outcomes support the conclusions based on the primary outcome (OS). Relative risk reductions in these other outcomes were in line with those observed in the OS analyses.

Similar restrictions to applicability apply to these outcomes as discussed in the OS section above.

Health-related quality of life

No evidence on HrQoL or disease-specific quality of life was available. This is considered to be a severe evidence gap from an HTA perspective and further research is needed to gain information on the effects of midostaurin on HrQoL and disease-specific quality of life.

Safety

The safety evaluation of midostaurin was mainly based on the RATIFY trial. All patients in the RATIFY trial experienced at least one AE of any grade regardless of its relation to the study drug. All except one patient in the midostaurin group experienced grade 3–4 AE(s). Approximately 50% of the patients in both groups experienced a SAE. 78% of patients in the midostaurin group and 75% of patients in placebo group reported at least one grade 3-4 AE considered related to treatment. Most events were reported during the induction and consolidation phases and events were less frequently reported during the continuation phase. There were 36 deaths on-treatment (i.e., within 30 days of the last treatment; 15 and 21 in the midostaurin and placebo arms, respectively). [C0008]

The most frequent grade 3–4 adverse events regardless of relationship to study drug were thrombocytopaenia, neutropaenia, anaemia and febrile neutropaenia. Grade 3-4 adverse events leading to discontinuation in more than one patient were dermatitis exfoliative, increased ALT, increased AST, decreased neutrophil count and renal failure in the midostaurin group and decreased platelet count, febrile neutropaenia and decreased neutrophil count in the placebo group. Overall, 23 (6.7%) patients in the midostaurin group and 17 (5.1%) patients in the placebo group discontinued therapy because of grade 3–4 AEs. [C0008]

Based on the safety results from the IIT trial, the treatment-related AEs and their severity were similar in patients aged ≤60 years and >60 years. The incidence of SAEs and discontinuation because of AEs were higher in older patients. Deaths occurred at a higher frequency in patients aged >60 years. [C0008].

Overall, AEs were balanced between groups but rates of grade 3–4 AEs were high. However, this is typical considering the health condition. Grade 3–4 AEs emerging more frequently in the midostaurin group than in the placebo group were exfoliative dermatitis and device-related infections. Furthermore, QTc prolongation has been observed in patients receiving midostaurin. [C0008]

Ethical, organisational, social and legal aspects

There were no potential concerns identified from an ethical, organisational, social or legal aspect that would be related to using midostaurin with standard induction and consolidation chemotherapy. All patients receiving midostaurin must be tested for FLT3 mutation. This testing might not be implemented Europe wide, which could have some impact on the resource use in some countries.

9 CONCLUSION

Midostaurin in combination with standard induction and consolidation chemotherapy is considered more effective than standard induction and consolidation chemotherapy alone in terms of improved OS in patients aged 18–60 years who are suitable for intensive chemotherapy. The risk of death was reduced by 23% during the follow-up for midostaurin versus placebo. The proportion of patients alive was significantly higher at the 1- and 5-year follow-ups, demonstrating both short- and long-term positive effects of midostaurin on survival. More uncertainty is related to the beneficial effects of midostaurin used in continuation therapy because of patient disposition in the trial leading to fewer patients receiving continuation therapy. Based on indirect comparison, there was insufficient evidence to determine whether midostaurin treatment was more beneficial than high-dose daunorubicin (90 mg/m^2) used during induction in terms of OS. Serious limitations apply to this comparison. Patients over 60-years old have not yet been studied in an RCT setting and the effect size of midostaurin on OS is unknown in this older population. However, age itself is not the limiting factor when using midostaurin, but rather patients' suitability for chemotherapy.

The safety profile of treatment with midostaurin is considered to be similar to that of standard induction and consolidation chemotherapy. However, grade 3–4 exfoliative dermatitis and device-related infections occurred more frequently in patients receiving midostaurin treatment. Furthermore, QTc prolongation has been observed in patients receiving midostaurin. Deaths during the study treatment period and 30-day follow-up period might occur more frequently in patients over 60-years old compared with younger patients.

Further research is needed (and is ongoing) to gain better understanding on the effects of midostaurin in the older population. Health-related quality of life and disease-specific quality of life should be studied, because this evidence is currently lacking.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search strategies used in MAH submission or related appendix [17]:

Embase search string

- Platform: Embase.com
- URL: www.embase.com
- Date searched: 07-Jun-2017
- Hits: 781

Table A1. Results for Embase search string.

No.	Query	Results
#1	'acute myeloid leukemia'/exp	88460
#2	'myeloid leukemia'/exp AND 'acute disease'/exp	1514
#3	**acut***:ab,ti OR **akut***:ab,ti OR **agud***:ab,ti OR **aigu***:ab,ti OR **akuut***:ab,ti	1398975
#4	((myelo* OR mielo* OR müelo* OR mjelo* OR nonlympho* OR 'non lymphocytic' OR granulocyt* OR monoblast* OR monocyt* OR 'di guglielmo' OR guglielmo* OR erythroid*) NEAR/3 (leukemi* OR leukaemi* OR leukämi* OR leukæmi* OR leukeemi* OR leuc* OR levkemi*)):ab,ti,de OR erythroleukemi*:ab,ti,de OR erythroleukaemi*:ab,ti,de	156573
#5	#3 AND #4	75735
#6	**aml**:ab,ti,de OR **anll**:ab,ti,de	49187
#7	**#1** OR **#2** OR **#5** OR **#6**	117467

#8	'cd135 antigen'/exp OR 'flt3 ligand'/exp OR 'gene mutation'/exp OR 'internal tandem duplication'/exp OR 'fms like tyrosine kinase 3 receptor'OR 'flt3 gene'/exp OR 'mutation'/exp	963230
#9	(**antigen** NEAR/3 **cd135**):ab,ti OR **flt3***:ab,ti OR **'flt 3'**:ab,ti OR (**fms*** NEAR/3 (**'tyrosine kinase 3'** OR **tk3** OR **'tk 3'**)):ab,ti OR (**fetal** NEAR/3 **liver**NEAR/3 **'tyrosine kinase 3'**):ab,ti OR (**stem** NEAR/3 **cell** NEAR/3 **'tyrosine kinase 1'**):ab,ti OR **stk1**:ab,ti OR **d835**:ab,ti OR **itd***:ab,ti OR **tkd***:ab,ti OR **kdm***:ab,ti OR **'kinase domain'**:ab,ti OR **rtk***:ab,ti OR (**receptor** NEAR/3 **tyrosine** NEAR/3 **kinase**):ab,ti OR ((**favourable*** OR **unfavourable***OR **favorable*** OR **unfavorable** OR **good** OR **intermediate*** OR **poor*** OR **adverse** OR **high*** OR **increase***) NEAR/3 (**risk*** OR **karyotype***)):ab,ti OR **fr**:ab,ti OR **'ir 1'**:ab,ti OR **'ir i'**:ab,ti OR **'ir 2'**:ab,ti OR **'ir ii'**:ab,ti	940838
#10	#8 OR #9	1853023
#11	(diagnos* NEAR/3 (new* OR recent*)):ab,ti OR '1st line':ab,ti OR ((first* OR initial) NEAR/3 (course* OR cycle* OR line* OR treatment* OR therap* OR regimen* OR induction*)):ab,ti OR frontline:ab,ti OR 'front line':ab,ti OR upfront:ab,ti OR naïve*:ab,ti OR 'treatment naïve':ab,ti OR treatmentnaive:ab,ti OR untreated:ab,ti OR 'un treated':ab,ti OR 'previously untreated':ab,ti OR 'not previously treated':ab,ti OR 'no previous':ab,ti OR 'no prior':ab,ti	683335
#12	'antileukemic agent'/exp OR 'anthracycline'/exp OR 'anthracycline derivative'/exp OR 'induction chemotherapy'/exp OR 'unclassified drug'/exp OR 'health care quality'/exp OR 'gold standard'/exp OR 'placebo'/exp OR 'protein kinase inhibitor'/exp OR 'cytarabine'/exp OR 'daunorubicin'/exp OR 'cytarabine plus daunorubicin'/exp OR 'idarubicin'/exp OR 'mitoxantrone'/exp OR 'sorafenib'/exp OR 'midostaurin'/exp OR 'lestaurtinib'/exp OR 'quizartinib'/exp OR 'crenolanib'/exp OR 'gilteritinib'/exp OR 'gemtuzumab'/exp OR 'gemtuzumab ozogamicin'/exp OR 'tosedostat'/exp OR 'clofarabine'/exp	5250514
#13	anthracyclin*:ab,ti OR cytarabin*:ab,ti OR 'ara c':ab,ti OR arac:ab,ti OR cytosin*:ab,ti OR hdac:ab,ti OR daunorubicin*:ab,ti OR idarubicin*:ab,ti OR mitoxantron*:ab,ti OR sorafenib*:ab,ti OR midostaurin*:ab,ti OR lestaurtinib*:ab,ti OR quizartinib*:ab,ti OR crenolanib*:ab,ti OR gilteritinib*:ab,ti OR gemtuzumab*:ab,ti OR tosedostat*:ab,ti OR clofarabin*:ab,ti OR 'cpx 351':ab,ti OR cpx351:ab,ti OR ((standard OR conventional) NEAR/3 (care OR therapy OR treatment* OR induction*)):ab,ti OR ((gold OR golden) NEAR/3 standard):ab,ti OR (soc NEAR/3 (standard OR care)):ab,ti OR placebo*:ab,ti OR ((induction OR intensive) NEAR/3 (chemotherapy OR therapy)):ab,ti OR ((fms OR flt3*) NEAR/4 inhibit*):ab,ti OR '5+2':ab,ti OR '5 + 2':ab,ti OR '5 plus 2':ab,ti OR '2+5':ab,ti OR '2 + 5':ab,ti OR '2 plus 5':ab,ti OR '3+7':ab,ti OR '3 + 7':ab,ti OR '3 plus 7':ab,ti OR '7+3':ab,ti OR '7 + 3':ab,ti OR '7 plus 3':ab,ti OR '10+3':ab,ti OR '10 + 3':ab,ti OR '10 plus 3':ab,ti OR '3+10':ab,ti OR '3 + 10':ab,ti OR '3 plus 10':ab,ti	1495763
#14	#12 OR #13	6205098
#15	'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'randomized controlled trial'/exp	507072
#16	**random***:ab,ti OR **factorial***:ab,ti OR **crossover***:ab,ti OR **'cross over'**:ab,ti OR (**cross** NEAR/1 **over***):ab,ti OR **placebo***:ab,ti OR ((**doubl*** OR **singl***) NEAR/1 **blind**):ab,ti OR **assign***:ab,ti OR **allocat***:ab,ti OR **volunteer***:ab,ti	1753268

#17	'randomized controlled trial':de	567401
#18	#15 OR #16 OR #17	1906287
#19	**#7** AND **#10** AND **#11** AND **#14** AND **#18**	673
#20	'practice guideline'/exp OR guideline*:ti OR recommendation*:ti OR standards:ti	477033
#21	'world health organization'/exp OR 'europe'/exp	1508338
#22	**europ***:ti,ca,cy OR **britain**:ti,ca,cy OR **british**:ti,ca,cy OR **england**:ti,ca,cy OR **english**:ti,ca,cy OR **scotland**:ti,ca,cy OR **scottish**:ti,ca,cy OR **'uk'**:ti,ca,cy OR **wales**:ti,ca,cy OR **welsh**:ti,ca,cy OR **'united kingdom'**:ti,ca,cy OR **uk**:ti,ca,cy OR **austria***:ti,ca,cy OR **albania***:ti,ca,cy OR **balkan**:ti,ca,cy OR **baltic**:ti,ca,cy OR **bosnia***:ti,ca,cy OR **bulgaria***:ti,ca,cy OR **croat***:ti,ca,cy OR **czech***:ti,ca,cy OR **hungary**:ti,ca,cy OR **hungarian**:ti,ca,cy OR **magyar***:ti,ca,cy OR **montenegro***:ti,ca,cy OR **poland**:ti,ca,cy OR **polish**:ti,ca,cy OR **romania***:ti,ca,cy OR **serbia***:ti,ca,cy OR **slovak***:ti,ca,cy OR **sloven***:ti,ca,cy OR **belgium**:ti,ca,cy OR **belgian**:ti,ca,cy OR **benelux**:ti,ca,cy OR **france**:ti,ca,cy OR **french**:ti,ca,cy OR **german***:ti,ca,cy OR **ireland**:ti,ca,cy OR **irish**:ti,ca,cy OR **liechtenstein**:ti,ca,cy OR **luxembourg***:ti,ca,cy OR **monaco**:ti,ca,cy OR **netherlands**:ti,ca,cy OR **dutch**:ti,ca,cy OR **scandinavia***:ti,ca,cy OR **nordic**:ti,ca,cy OR **norway**:ti,ca,cy OR **norwegian**:ti,ca,cy OR **sweden**:ti,ca,cy OR **swedish**:ti,ca,cy OR **denmark**:ti,ca,cy OR **danish**:ti,ca,cy OR **finland**:ti,ca,cy OR **finnish**:ti,ca,cy OR **greenland**:ti,ca,cy OR **iceland***:ti,ca,cy OR **greece**:ti,ca,cy OR **greek**:ti,ca,cy OR **hellenic**:ti,ca,cy OR **spain**:ti,ca,cy OR **spanish**:ti,ca,cy OR **italy**:ti,ca,cy OR **italian**:ti,ca,cy OR **portugal**:ti,ca,cy OR **portuguese**:ti,ca,cy OR **switzerland**:ti,ca,cy OR **swiss**:ti,ca,cy	11054499
#23	#21 OR #22	11713186
#24	**acut***:ti OR **akut***:ti OR **agud***:ti OR **aigu***:ti OR **akuut***:ti	573244
#25	((myelo* OR mielo* OR müelo* OR mjelo* OR nonlympho* OR 'non lymphocytic' OR granulocyt* OR monoblast* OR monocyt* OR 'di gugliel-mo' OR guglielmo* OR erythroid*) NEAR/3 (leukemi* OR leukaemi* OR leukämi* OR leukæmi* OR leukeemi* OR leuc* OR levkemi*)):ti OR erythroleukemi*:ti OR erythroleukaemi*:ti	58103
#26	**aml**:ti OR **anll**:ti	8696
#27	#24 AND #25 OR #26	37107
#28	**#20** AND **#23** AND **#27** AND [2006-2017]/py	158

#29	pediatric:ti OR paediatric:ti OR child*:ti NOT adult:ti	951827
#30	#28 NOT #29	124
#31	**#19** OR **#30** AND [embase]/lim	781

Medline search string

- Platform: Pubmed
- URL: http://www.ncbi.nlm.nih.gov/pubmed/
- Date searched: 7-Jun-2017
- Hits: 558

Table A2. Results for Medline search string

Search	Query	Items found
#1	Search "Leukemia, Myeloid, Acute"[mh]	48387
#2	Search ("Leukemia, Myeloid"[mh] AND "Acute Disease"[mh])	7773
#3	Search (acut*[tiab] OR akut*[tiab] OR agud*[tiab] OR aigu*[tiab] OR akuut*[tiab])	1035579
#4	Search (((myelo*[tiab] OR mielo*[tiab] OR müelo*[tiab] OR mjelo*[tiab] OR nonlympho*[tiab] OR "non lymphocytic"[tiab] OR granulocyt*[tiab] OR mono-blast*[tiab] OR monocyt*[tiab] OR "Di Guglielmo"[tiab] OR Guglielmo*[tiab] OR erythroid*[tiab]) AND (leukemi*[tiab] OR leukaemi*[tiab] OR leukämi*[tiab] OR leukæmi*[tiab] OR leukeemi*[tiab] OR leuc*[tiab] OR levkemi*[tiab])) OR erythroleukemi*[tiab] OR erythroleukaemi*[tiab])	98720
#5	Search (#3 AND #4)	51919
#6	Search (aml[tiab] OR anll[tiab])	27292
#7	Search (#1 OR #2 OR #5 OR #6)	80527

#8	Search ("fms-Like Tyrosine Kinase 3"[mh] OR "FLT3 protein, human"[supplementary concept] OR "flt3 ligand protein"[supplementary concept] OR “mutation”[mh])	669537
#9	Search ((antigen[tiab] AND cd135[tiab]) OR flt3*[tiab] OR “flt 3”[tiab] OR (fms*[tiab] AND (“tyrosine kinase 3”[tiab] OR TK3[tiab] OR “TK 3”[tiab])) OR (fetal[tiab] AND liver[tiab] AND “tyrosine kinase 3”[tiab]) OR (stem[tiab] AND cell[tiab] AND “tyrosine kinase 1”[tiab]) OR STK1[tiab] OR D835[tiab] OR ITD*[tiab] OR TKD*[tiab] OR KDM*[tiab] OR “kinase domain”[tiab] OR RTK*[tiab] OR (receptor[tiab] AND tyrosine[tiab] AND kinase[tiab]) OR ((favourable*[tiab] OR unfavourable*[tiab] OR favorable*[tiab] OR unfavorable[tiab] OR good[tiab] OR intermediate*[tiab] OR poor*[tiab] OR adverse[tiab] OR high*[tiab] OR increase*[tiab]) AND (risk*[tiab] OR karyotype*[tiab])) OR FR[tiab] OR “IR 1”[tiab] OR “IR I”[tiab] OR “IR 2”[tiab] OR “IR II”[tiab])	1303329
#10	Search (#8 OR #9)	1930908
#11	Search ((diagnos*[tiab] AND (newly[tiab] OR recent*[tiab])) OR “1st line”[tiab] OR ((first*[tiab] OR initial[tiab]) AND (course*[tiab] OR cycle*[tiab] OR line[tiab] OR treatment*[tiab] OR therap*[tiab] OR regimen*[tiab] OR induction*[tiab])) OR frontline[tiab] OR “front line”[tiab] OR upfront[tiab] OR naïve*[tiab] OR “treatment naïve”[tiab] OR treatmentnaive[tiab] OR untreated[tiab] OR “un treated”[tiab] OR “previously untreated”[tiab] OR “not previously treated”[tiab] OR “no previous”[tiab] OR “no prior”[tiab])	1345605
#12	Search (“Anthracyclines”[mh] OR "Induction Chemotherapy"[mh] OR "Quality of Health Care"[mh] OR “placebos”[mh] OR "Protein Kinase Inhibitors"[mh] OR "Protein Kinase Inhibitors" [pharmacological action] OR "Cytarabine"[mh] OR “mitoxantrone”[mh] OR “sorafenib”[supplementary concept] OR “midostaurin”[supplementary concept] OR “lestaurtinib”[supplementary concept] OR “quizartinib”[supplementary concept] OR “crenolanib”[supplementary concept] OR “gemtuzumab”[supplementary concept] OR “tosedostat”[supplementary concept] OR “clofarabine”[supplementary concept])	5942832
#13	Search (anthracyclin*[tiab] OR cytarabin*[tiab] OR “ara C”[tiab] OR araC[tiab] OR cytosine[tiab] OR HDAC[tiab] OR daunorubicin*[tiab] OR idarubicin*[tiab] OR mitoxantron*[tiab] OR sorafenib*[tiab] OR midostaurin*[tiab] OR lestaurtinib*[tiab] OR quizartinib*[tiab] OR crenolanib*[tiab] OR gilteritinib*[tiab] OR gemtuzumab*[tiab] OR tosedostat*[tiab] OR clofarabin*[tiab] OR ((standard[tiab] OR conventional[tiab]) AND (care[tiab] OR therapy[tiab] OR treatment*[tiab] OR induction*[tiab])) OR ((gold[tiab] OR golden[tiab]) AND standard[tiab]) OR (SOC[tiab] AND (standard[tiab] OR care[tiab])) OR placebo*[tiab] OR ((induction[tiab] OR intensive[tiab]) AND (chemotherapy[tiab] OR therapy[tiab])) OR ((fms[tiab] OR flt3*[tiab]) AND inhibit*[tiab]) OR “5+2”[tiab] OR “5 + 2”[tiab] OR “5 plus 2”[tiab] OR “2+5”[tiab] OR “2 + 5”[tiab] OR “2 plus 5”[tiab] OR “3+7”[tiab] OR “3 + 7”[tiab] “3 plus 7”[tiab] OR “7+3”[tiab] OR “7 + 3”[tiab] OR “7 plus 3”[tiab] OR “10+3”[tiab] OR “10 + 3”[tiab] OR “10 plus 3”[tiab] OR “3+10”[tiab] OR “3 + 10”[tiab] OR “3 plus 10”[tiab])	170618
#14	Search (#12 OR #13)	6047106
#15	Search (“randomized controlled trial”[pt] OR “controlled clinical trial”[pt] OR randomized[tiab] OR randomised[tiab] OR placebo*[tiab] OR randomly[tiab] OR trial[ti])	1001004
#16	Search clinical trials as topic [mh:NoExp]	179646

#17	Search (#15 OR #16)	1125684
#18	Search (#7 AND #10 AND #11 AND #14 AND #17)	490
#19	Search (“practice guideline”[pt] OR "Practice Guidelines as Topic"[mh])	119865
#20	Search (guideline*[ti] OR recommendation*[ti] OR standards[ti])	111646
#21	Search (#19 OR #20)	189170
#22	Search (“world health organization”[mh] OR “Europe”[mh])	1271609
#23	Search (Europ*[tiabtw] OR britain[tiabtw] OR British[tiabtw] OR England[tiabtw] OR English[tiabtw] OR Scotland[tiabtw] OR Scottish[tiabtw] or “UK”[tiabtw] OR wales[tiabtw] OR Welsh[tiabtw] OR “United Kingdom”[tiabtw] OR UK[tiabtw] OR Austria*[tiabtw] OR Albania*[tiabtw] OR Balkan[tiabtw] OR Baltic[tiabtw] OR Bosnia*[tiabtw] OR Bulgaria*[tiabtw] OR Croat*[tiabtw] OR Czech*[tiabtw] OR Hungary[tiabtw] OR Hungarian[tiabtw] OR Magyar*[tiabtw] OR Montenegro*[tiabtw] OR Poland[tiabtw] OR Polish[tiabtw] OR Romania*[tiabtw] OR Serbia*[tiabtw] OR Slovak*[tiabtw] OR Sloven*[tiabtw] OR Belgium[tiabtw] OR Belgian[tiabtw] OR Benelux[tiabtw] OR France[tiabtw] OR French[tiabtw] OR German[tiabtw] OR Germany[tiabtw] OR Ireland[tiabtw] OR Irish[tiabtw] OR Liechtenstein[tiabtw] OR Luxembourg*[tiabtw] OR Monaco[tiabtw] OR Netherlands[tiabtw] OR Dutch[tiabtw] OR Scandinavia*[tiabtw] OR Nordic[tiabtw] OR Norway[tiabtw] OR Norwegian[tiabtw] OR Sweden[tiabtw] OR Swedish[tiabtw] OR Denmark[tiabtw] OR Danish[tiabtw] OR Finland[tiabtw] OR Finnish[tiabtw] OR Greenland[tiabtw] OR Iceland*[tiabtw] OR Greece[tiabtw] OR Greek[tiabtw] OR Hellenic[tiabtw] OR spain[tiabtw] OR Spanish[tiabtw] OR Italy[tiabtw] OR Italian[tiabtw] OR Portugal[tiabtw] OR Portuguese[tiabtw] OR Switzerland[tiabtw] or Swiss[tiabtw])	26237182
#24	Search (#22 OR #23)	26264239
#25	Search (acut*[ti] OR akut*[ti] OR agud*[ti] OR aigu*[ti] OR akuut*[ti])	438679
#26	Search (((myelo*[ti] OR mielo*[ti] OR müelo*[ti] OR mjelo*[ti] OR nonlympho*[ti] OR “non lymphocytic”[ti] OR granulocyt*[ti] OR monoblast*[ti] OR monocyt*[ti] OR “Di Guglielmo”[ti] OR Guglielmo*[ti] OR erythroid*[ti]) AND (leukemi*[ti] OR leukaemi*[ti] OR Leukämi*[ti] OR leukæmi*[ti] OR leukeemi*[ti] OR leuc*[ti] OR levkemi*[ti])) OR erythroleukemi*[ti] OR erythroleukaemi*[ti])	46939
#27	Search (#25 AND #26)	23446
#28	Search (aml[ti] OR anll[ti])	3574
#29	Search (#27 OR #28)	26182

#30	Search (#21 AND #24 AND #29)	72
#31	Search (paediatric[ti] OR pediatric[ti] OR child*[ti])	767055
#32	Search (#30 NOT #31)	68
#33	Search (#18 OR #32)	558

CENTRAL search string

- Platform: Cochrane Library
- URL: http://onlinelibrary.wiley.com/cochranelibrary/search/
- Date searched: 7-Jun-2017
- Hits: 282

Table A3. Results for CENTRAL search string

ID	Search	Hits
#1	MeSH descriptor: [Leukemia, Myeloid, Acute] explode all trees	987
#2	MeSH descriptor: [Leukemia, Myeloid] explode all trees	1666
#3	MeSH descriptor: [Acute Disease] explode all trees	9680
#4	#2 and #3	288
#5	(acut* or akut* or agud* or aigu* or akuut*):ti,ab,kw	90696
#6	(((myelo* or mielo* or müelo* or mjelo* or nonlympho* or "non lymphocytic" or granulocyt* or monoblast* or monocyt* or "Di Guglielmo" or Guglielmo* or erythroid*) near/3 (leukemi* or leukaemi* or Leukämi* or leukæmi* or leukeemi* or leuc* or levkemi*)) or erythroleukemi* or erythroleukaemi*):ti,ab,kw	4334

#7	#5 and #6	3269
#8	(aml or anll):ti,ab,kw	2397
#9	#1 or #4 or #7 or #8	4064
#10	MeSH descriptor: [fms-Like Tyrosine Kinase 3] explode all trees	28
#11	MeSH descriptor: [Mutation] explode all trees	2211
#12	((antigen near/3 cd135) or flt3* or "flt 3" or (fms* near/3 ("tyrosine kinase 3" or TK3 or "TK 3")) or (fetal near/3 liver near/3 "tyrosine kinase 3") or (stem near/3 cell near/3 "tyrosine kinase 1") or STK1 or D835 or ITD* or TKD* or KDM* or "kinase domain" or RTK* or (receptor near/3 tyrosine near/3 kinase) or ((favour-able* or unfavourable* or favorable* or unfavorable or good or intermediate* or poor* or adverse or high* or increase*) near/3 (risk* or karyotype*)) or FR or "IR 1" or "IR I" or "IR 2" or "IR II"):ti,ab,kw	54832
#13	#10 or #11 or #12	56781
#14	((diagnos* near/3 (new* or recent*)) or "1st line" or ((first* or initial) near/3 (course* or cycle* or line* or treatment* or therap* or regimen* or induction*)) or frontline or "front line" or upfront or naïve* or "treatment naïve" or treatmentnaive or untreated or "un treated" or "previously untreated" or "not previously treated" or "no previous" or "no prior"):ti,ab,kw	54944
#15	MeSH descriptor: [Anthracyclines] explode all trees	4361
#16	MeSH descriptor: [Induction Chemotherapy] explode all trees	240
#17	MeSH descriptor: [Quality of Health Care] explode all trees	424283
#18	MeSH descriptor: [Placebos] explode all trees	23271
#19	MeSH descriptor: [Protein Kinase Inhibitors] explode all trees	687
#20	MeSH descriptor: [Cytarabine] explode all trees	916
#21	MeSH descriptor: [Mitoxantrone] explode all trees	400
#22	(anthracyclin* or cytarabin* or "ara C" or araC or cytosin* or HDAC or daunorubicin* or idarubicin* or mitoxantron* or sorafenib* or midostaurin* or les-taurtinib* or quizartinib* or crenolanib* or gilteritinib* or gemtuzumab* or tosedostat* or clofarabin* or "CPX 351" or CPX351 or ((standard or conventional)	283010

	near/3 (care or therapy or treatment* or induction*)) or ((gold or golden) near/3 standard) or (SOC near/3 (standard or care)) or placebo* or ((induction or intensive) near/3 (chemotherapy or therapy)) or ((fms or flt3*) near/4 inhibit*) or "5+2" or "5 + 2" or "5 plus 2" or "2+5" or "2 + 5" or "2 plus 5" or "3+7" or "3 + 7" or "3 plus 7" or "7+3" or "7 + 3" or "7 plus 3" or "10+3" or "10 + 3" or "10 plus 3" or "3+10" or "3 + 10" or "3 plus 10"):ti,ab,kw	
#23	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	567752
#24	#9 and #13 and #14 and #23	291
#25	MeSH descriptor: [Practice Guideline] explode all trees	16
#26	MeSH descriptor: [Practice Guidelines as Topic] explode all trees	2071
#27	(guideline* or recommendation* or standards):ti	4160
#28	#25 or #26 or #27	5501
#29	MeSH descriptor: [World Health Organization] explode all trees	301
#30	MeSH descriptor: [Europe] explode all trees	26835
#31	(Europ* or britain or British or England or English or Scotland or Scottish or "UK" or wales or Welsh or "United Kingdom" or UK or Austria* or Albania* or Balkan or Baltic or Bosnia* or Bulgaria* or Croat* or Czech* or Hungary or Hungarian or Magyar* or Montenegro* or Poland or Polish or Romania* or Serbia* or Slovak* or Sloven* or Belgium or Belgian or Benelux or France or French or German* or Ireland or Irish or Liechtenstein or Luxembourg* or Monaco or Netherlands or Dutch or Scandinavia* or Nordic or Norway or Norwegian or Sweden or Swedish or Denmark or Danish or Finland or Finnish or Greenland or Iceland* or Greece or Greek or Hellenic or spain or Spanish or Italy or Italian or Portugal or Portuguese or Switzerland or Swiss):ti,ab,kw	117957
#32	#29 or #30 or #31	119088
#33	(acut* or akut* or agud* or aigu* or akuut*):ti	47031
#34	(((myelo* or mielo* or müelo* or mjelo* or nonlympho* or "non lymphocytic" or granulocyt* or monoblast* or monocyt* or "Di Guglielmo" or Guglielmo* or erythroid*) near/3 (leukemi* or leukaemi* or Leukämi* or leukæmi* or leukeemi* or leuc* or levkemi*)) or erythroleukemi* or erythroleukaemi*):ti	2812
#35	#33 and #34	1958
#36	(aml or anll):ti	1117

#37	#35 or #36	2557
#38	#28 and #32 and #37	0
#39	#24 or #38	291
#40	#39 in Trials	282

Details of hand searches

Table A4. Conferences included in the literature search

Research meeting	Keywords	Hits	Relevant
58th ASH Annual Meeting December 2016	acute myeloid leukemia, acute myelogenous leukemia, acute myeloblastic leukaemia, FLT3	106	1
21st EHA Congress 9-12 June 2016, Copenhagen, Denmark	acute myeloid leukemia	108	4
22nd EHA Congress 22-25 June 2017, Madrid, Spain	acute myeloid leukemia	132	1

Table A5. Registries included in the literature search (26th June 2017)

Database	Search strategy	Hits	Relevant
US NIH registry & results database	Advanced search Search terms: FLT3 / Condition: acute myeloid leukaemia OR FLT3	116	3
WHO ICTRP registry	Advanced search Search terms: FLT3* in Title AND acute myeloid leuk* OR FLT3* in Condition Recruitment status: ALL	56	1
EU Clinical Trial Registry	Basic search Search terms: acute myeloid leuk* AND FLT3*	41	3

Additional results of searches

Table A6. HTA-websites literature search

Database	Keywords	Hits	Relevant
NICE	FLT3, acute myeloid leukemia	22	3
HAS	FLT3, acute myeloid leukemia	18	1
SBU	FLT3, acute myeloid leukemia	0	0
G-BA	FLT3, acute myeloid leukemia	71	0

Abbreviations: see list of abbreviations.

Table A7. HTA websites relevant hits

Health Technology Assessment (HTA) site	Source	Name of the document
NICE	https://www.nice.org.uk/guidance/gid-ta10124/documents/scope-consultation-comments-and-responses	Midostaurin for untreated acute myeloid leukaemia [ID894].
	https://www.nice.org.uk/guidance/indevelopment/gid-ta10142	Gemtuzumab ozogamicin for untreated de novo acute myeloid leukaemia [ID982].
HAS	https://www.has-sante.fr/portail/jcms/c_401011/en/zavedos?xtmc=&xtcr=2	Zavedos.

Abbreviations: see List of abbreviations.

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A8: Overview of guidelines

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
[50]	2006	UK	**Diagnosis** Bone marrow aspirate, bone marrow trephine biopsy; immunophenotyping; cytochemistry; cytogenetics	
			Management **Induction** Intensive: cytarabine + daunorubicin Nonintensive: LDAC BSC: transfusion support + hydroxycarbamide	**A/Ib**
			Consolidation Chemotherapy + SCT	**A/Ib** **Unclear for SCT**
			Salvage therapy Cytarabine (low, intermediate, or high doses) ± other drugs (e.g., fludarabine, daunorubicin + etoposide)	**B/IIb**
[26]	2013	Europe	**Diagnosis** Morphology, cytochemistry, immunophenotyping, cytogenetics and molecular genetics work up on peripheral blood and bone marrow specimens	

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
			Management **Induction** Cytarabine + daunorubicin (± hematopoietic growth factors) BSC: LDAC or decitabine or azacitidine	**A/I**
			Consolidation IDAC or HDAC in good-risk patients SCT in patients with intermediate- to poor-risk AML provided age and PS make the patient eligible	**A/I**
			Salvage Re-induction SCT BSC	**B/II**

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
[33]	2017	Europe	**Diagnosis** Complete blood count and differential count; bone marrow aspirate, bone marrow trephine biopsy; immunophenotyping Genetic analysis **Management of patients eligible for intensive CT** **Induction** Anthracycline plus cytarabine: 3 days of an anthracycline: daunorubicin ≥60 mg/m^2, idarubicin 12 mg/m^2, or mitoxantrone 12 mg/m^2 plus 7 days of cytarabine, 100–200 mg/m^2 continuous infusion **Consolidation** 18–65 years favourable-risk genetics: IDAC 18–65 years intermediate-risk genetics: alloSCT; IDAC or HDCT plus autologous SCT 18–65 years adverse-risk genetics: alloSCT >60/65 years favourable-risk genetics: IDAC >60/65 years intermediate/adverse-risk genetics: consider alloSCT or investigational therapy **Management of patients ineligible for intensive CT** Azacitadine, decitabine, LDAC, BSC **Salvage regimens** IDAC (with or without anthracycline) FLAG-IDA MEC AlloSCT	**Not stated in publication**
[49]	2009	Italy	**Induction** Standard induction therapy: cytarabine + daunorubicin, idarubicin or mitoxantrone But not recommended for: >80 years, severe comorbidity or poor PS who should receive cytoreductive therapy (attenuated doses and/or oral admin-	**A**

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
			istration) and/or experimental therapies with significantly lower non-haematologic toxicities	**B**
			Patients >65 years and not eligible for SCT should receive experimental therapies with limited non-haematologic toxicities, cytoreductive agents and BSC **Consolidation**	**B**
			Patients in first complete response should receive a consolidation treatment as soon as the haematologic recovery from induction therapy has occurred **Adults <60 years** should receive post-remission consolidation chemotherapy based on HDAC; the number of cycles should not exceed 3–4	**D**

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
			Potential candidates for allogeneic SCT should receive a shorter intensive consolidation including IDAC/HDAC in order to spare undue toxicity **Potential candidates for autologous SCT** should receive at least one intensive consolidation cycle including IDAC/HDAC before collecting stem cells and performing autograft **Elderly patients (>60 years)** should not receive HDAC-based consolidation therapy and no more than two consolidation cycles **AlloSCT consolidation** From fully matched sibling donor is recommended in first CR for: 1) adults with high-risk cytogenetics provided that they are aged <55 years and do not carry severe comorbidities 2) adult patients with intermediate-risk cytogenetics with the exception of NPM1 mutation and FLT3-ITD-negative cases, provided that they are aged under 40 years and do not carry severe comorbidities 3) patients who achieved a first CR only after having received a second course of induction therapy, irrespectively of their cytogenetic risk, provided that they are aged under 55 years and do not carry severe comorbidities AlloSCT from unrelated donor (if no fully matched sibling donor available) is	**D**

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
			recommended for all adult patients in first complete response aged under 30 years with high-risk cytogenetics, or who achieved first CR only after a second course of induction therapy **Autologous SCT consolidation** Consolidation autologous SCT is recommended for patients eligible for high-dose chemotherapy who are not candidates for allogeneic SCT from a fully HLA-matched donor	**D**
[24]	2016	Norway	**Diagnosis** Morphological examination of bone marrow smear after MGG staining Cytochemical staining of bone marrow smears In patients with induction treatment with a view to complete remission, ghd is required as well:	
			Cytogenetic examination of bone marrow cells Molecular genetic examination of bone marrow cells Flow cytomy with immune phenotyping of bone marrow cells	A
			Management induction phase **<65 years**	A
			daunorubicin 90 mg/m^2 daily for 3 days or idarubicin 12 mg/m^2 daily for 3 days, both in combination with cytarabine 200 mg/m^2 body surface/day as a	A

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
			continuous infusion for 7 days. **>65 years** after individual assessment daunorubicin 60 mg/m²/day for 3 days and cytarabine 200 mg/m²/day for 7 days	A/B
			Consolidation	B
			Up to 60 years: HDAC (3 g/m² days 1,3 and 5) or treatment according HOVONSAKK protocol cytarabine + daunorubicin **>65 years** **STC should be considered** Patients up to 70 years of age who have a suitable family provider and yet not transplanted in the first remedy may be candidates for allogeneic stem cell transplant at the beginning of their stay and should therefore be closely monitored while in first remission **Consolidation**: Mitoxantrone, amsacrine, etoposide, or Daunorubicin + cytarabine, azacitidine, or cytarabine **>65 years ineligible for intensive chemotherapy** – palliative care	C

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
[23]	2017	USA	**<60 years** **Induction**: clinical trial, cytarabine plus idarubicin or daunorubicin ± cladribine; or HDAC + idarubicin or daunorubicin; cytarabine + daunorubicin + midostaurin; or fludarabine + HDAC + idarubicin + G-CSF **CR: consolidation**, i.e., HDAC, trial, or SCT Induction failure: trial, matched SCT or HDAC ± anthracycline or BSC **Consolidation**: Favourable-risk genetics: trial or HDAC Intermediate-risk genetics: trial, alloSCT or **HDAC** Poor-risk genetics: trial, alloSCT **≥60 years and eligible for intensive therapy** **Induction:** Without unfavourable genetic risk: trial, cytarabine + idarubicin or daunorubicin or mitoxantrone With unfavourable genetic risk: trial, or 5-azacytidine or decitabine or cytarabine with idarubicin/daunorubicin/mitoxantrone, or clofarabine **Consolidation**: CR: trial, cytarabine ± anthracycline or IDAC or 5-azacytidine or decitabine Induction failure: trial, alloSCT, BSC	**Most recommendations are class 2A**

Name of society/organisation issuing guidelines	Date of issue or last update	Countries to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)	Level of evidence (A, B, C)/ class of recommendation (I, IIa, IIb, III)
Nationellt vårdprogram Akut myeloisk leukemi 2016 **http://www.sfhem.se/nyheter/nationellt-vardprogram-aml**. **http://www.sfhem.se/riktlinjer**	2016	Sweden	Induction & consolidation therapy **Cyclus 1 & 2 (DA3+5)** **Day** **Daunorubicin 60 mg/m² × 1 iv infusion 8 h 1, 2, 3** **Cytarabin 1 g/m² × 2 iv infusion 2 h 1, 2, 3, 4, 5** **Cyclus 3 (DA2+5)** **Daunorubicin 60 mg/m² × 1 iv infusion 8 h 1, 2** **Cytarabin 1 g/m² × 2 iv infusion 2 h 1, 2, 3, 4, 5** **Cyclus 5 (DA** **Cytarabin 1 g/m² × 2 iv infusion 2 h 1, 2, 3, 4, 5** **Patient not responding for induction therapy** **Azacitidine 75 mg/m² s.c. 1-7**	

Abbreviations: see List of abbreviations.

Evidence tables of individual studies included for clinical effectiveness and safety

Table A9: Characteristics of randomised controlled studies

Trial number (acronym)	**CPKC412A2301, CALGB 10603 (RATIFY)**
Location	Multicentre international study; 225 sites in 17 countries (including Australia, Canada, Germany, Italy, the Netherlands, Spain, the US). A total of 3277 patients were screened in 17 countries but only 13 countries randomised patients: Australia (2), Austria (12), Belgium (8), Canada (13), Czech Republic (11), France (5), Germany (305) Hungary (2), Italy (105), The Netherlands (5), Slovakia (4), Spain (22), US (223).
Trial design	A phase III, 1:1 randomised, double-blind, placebo-controlled trial Patients stratified by FLT3 mutation subtype (TKD vs. ITD high allelic mutation fraction [≥0.7] vs. ITD low mutation fraction [<0.7])
Eligibility criteria for participants	Inclusion criteria • Unequivocal diagnosis of AML (>20% blasts in the bone marrow based on the WHO classification, excluding M3 [acute promyelocytic leukaemia]) • Documented FLT3 mutation (ITD or TKD), determined by analysis in a protocol-designated FLT3 screening laboratory • Age ≥18 and <60 years • No prior chemotherapy for leukaemia or myelodysplasia (exceptions: emergency leukapheresis, emergency treatment for hyperleukocytosis with hydroxyurea for ≤5 days, single dose of cranial radiation therapy for central nervous system leukostasis, growth factor/cytokine support) Exclusion criteria • AML blasts in the CSF (in patients with symptoms suggestive of CNS leukaemia) • Therapy-related AML after prior radiation therapy or chemotherapy for another cancer or disorder • Symptomatic congestive heart failure • Total bilirubin ≥2.5 × ULN • History of antecedent MDS in patients who had prior cytotoxic therapy (e.g., azacitidine or decitabine) • Pregnant or nursing patients

Trial number (acronym)	**CPKC412A2301, CALGB 10603 (RATIFY)**
Settings and locations where the data were collected	Secondary care (hospital) setting
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Permitted and disallowed concomitant medication**	Interventional arm, n=360 Comparator arm, n=357 Induction phase (1–2 cycles): IV cytarabine 200 mg/m^2/day (days 1–7) + IV daunorubicin 60 mg/m^2/day (days 1–3) + oral Rydapt® 50 mg BID (days 8–21) Consolidation phase (4 cycles): IV cytarabine 3 g/m^2 every 12 hours (days 1–7) + oral Rydapt® 50 mg BID (days 8–21) Maintenance phase (up to 12 cycles): oral Rydapt® 50 mg BID (days 1–28) Concomitant therapy: • Patients were to receive dexamethasone 0.1% or corticosteroid ophthalmic solution starting 6–12 hours prior to the initiation of the high-dose cytarabine infusion and therapy was to be continued for at least 24 hours after the last cytarabine dose • Patients were to receive full supportive care, including blood transfusions and products • Myeloid growth factors were not to be used routinely or prophylactically, but were permitted as indicated by the American Society of Clinical Oncology guidelines for neutropenic patients; use of growth factors was to be documented Use of the following concomitant drugs was to be recorded: Antibiotic/antiviral/antifungal agents, proton pump inhibitors or H_2-receptor antagonists, nonsteroidal anti-inflammatory drugs, opioids, antiemetic agents, antihistamines, corticosteroids, growth factors, diuretics, antihypertensives, and other CYP3A4 inhibitors and CYP3A4 inducers Disallowed concomitant drugs: • Hormones, except for steroids given for adrenal failure or to treat and/or prevent hypersensitivity reactions or transfusion reactions and hormones administered for non-disease-related conditions • Other chemotherapeutic agents

Trial number (acronym)	CPKC412A2301, CALGB 10603 (RATIFY)
	Patients who underwent SCT were not to resume Rydapt®/placebo therapy
Primary outcomes (including scoring methods and timings of assessments)	OS

Secondary/tertiary outcomes (including scoring methods and timings of assessments)	• Key secondary objective: EFS
	• Other secondary endpoints:
	  • CR
	  • DFS
	  • CIR
	• OS, EFS and DFS censored at time of SCT
	• Safety (frequency and severity of adverse events and laboratory abnormalities)

Pre-planned subgroups	Subgroups defined based on baseline characteristics • **FLT3 mutation status 1 (stratification factor)**: TKD mutation-positive patients, ITD mutation-positive patients with allelic ratio <0.7, ITD mutation-positive patients with allelic ratio ≥0.7 • **FLT3 mutation status 2**: TKD mutation-positive patients, ITD mutation-positive patients with allelic ratio <0.50, ITD mutation-positive patients with allelic ratio ≥0.50 • **FLT3 mutation subtype**: TKD mutation-positive patients vs. ITD mutation-positive patients • **Gender** • **Region**: North America vs. non-North America • **Prior MDS**: Yes vs. No • **Cytogenetic profile**: AML with t(8;21) (q22; q22), AML with inv(16) (p13; q22) or t(16;16) (p13; q22), AML with 11q23 (MLL) abnormalities, other • **WBC count at baseline**: $<50 \times 10^9$/L vs. $\geq 50 \times 10^9$/L • **Race**: Asian, Black or African American, White, Other (American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, other, unknown, more than one race) • **ECOG Performance Status**: 0–1 vs. ≥2
Hypothesis objective	To evaluate the effect on OS of adding Rydapt® to standard chemotherapy (induction therapy –daunorubicin/cytarabine – and consolidation therapy – high-dose cytarabine), followed by Rydapt® monotherapy in patients with newly diagnosed FLT3 mutation-positive AML
Statistical analysis	• Stratified log-rank tests adjusting for the FLT3 mutation strata were used to test the null hypothesis and calculate the one-sided p-value

Trial number (acronym)	CPKC412A2301, CALGB 10603 (RATIFY)
	• Stratified Cox regression models adjusting for FLT3 mutation were used to estimate HRs and Wald 95% CIs • Kaplan–Meier plots were used to depict time to event endpoints • Median survival time and 95% CIs were calculated using the method of Brookmeyer and Crowley (1982)97 • Kaplan–Meier estimates with 95% CIs at specific time points were summarized using Greenwood's formula for the standard error of the Kaplan–Meier estimate • CR rates were compared using Cochran-Mantel-Haenszel test stratified for FLT3 mutation strata at one-sided 2.5% level
Sample size, power calculation	• Initial protocol: 514 patients and 374 events were estimated to be necessary to attain a 90% power with an accrual period of 1.7 years (i.e., 20.5 months) and a follow-up period of 2.0 years (i.e., 24 months) after accrual termination assuming an HR of 0.71. (Median OS: placebo, 15 months; midostaurin, 21 months) • The protocol was amended in December 2010, on the basis of a review of the blinded data, which indicated a higher than expected rate of randomisation of FLT3-TKD patients (increased from 14% to 26%) and a higher percentage of patients undergoing SCT (increased from 15% to 25%). The sample size was thus increased to accrue a total of 714 patients, with a 2.9-year accrual period and 1.6-year follow-up period from the time the last patient was randomised. A total of 509 OS events were expected by May 2013, to attain a power of 84% for the ITT analysis on OS to detect a HR of 0.78 with a one-sided test at an overall one-sided alpha level of 2.5%
Data management, patient withdrawals	• Patients who discontinued study treatment remained in the study and were followed up for response status (if in CR when discontinuing), long-term survival and SCT status • Patients who were prematurely withdrawn from the study were not replaced by newly enrolled patients • Patients with an up-to-date vital status and who were alive on or after 01 April 2015 were censored for the OS analysis. Patients indicated as being dead after 1st April 2015 were censored on 1st April 2015 in the primary analysis

Abbreviations: see List of abbreviations.
Sources: [17]

Table A10: Characteristics of other relevant studies

Primary reference source	**Study type**	**Number of patients**	**Intervention(s)**	**Comparator (Number of patients)** **If applicable**	**Patient population**	**Endpoints**	**Duplicate publications from the same study**
Investigator-initiated trial (AMLSG 16-10.CPKC412ADE02T); primary reference: **[17]**	Phase II single-arm, multicentre, investigator-initiated study	n=145	Midostaurin plus daunorubicin plus cytarabine	NA	• Patients aged 18–70 years with newly diagnosed FLT3-ITD-positive AML • WHO Performance Status of ≤2 • Considered eligible for intensive chemotherapy and had received no prior chemotherapy for leukaemia except hydroxyurea to control hyperleukocytosis (received for ≤7 days)	EFS Other: • CR • RFS • OS	[19, 20]
UK NCRI AML17 trial	Phase III randomised controlled trial	Daunorubicin 90 mg/m^2 n=604 (100	**Daunorubicin 90mg/m^2** (d1,3,5) in course 1, then	**Daunorubicin 60mg/m^2** (d1,3,5) in course 1, then	Patients with any form of AML (excluding acute	OS (3-year follow-up)	[10]

primary reference: **[10, 11]**		with FLT3 ITD) Daunorubicin 60 mg/m^2 n=602 (100 with FLT3 ITD)	50mg/m^2 (d1,3,5) in course 2, with Ara-C 100mg/m^2 12-hourly d1-10 (course 1) and d1-8 (course 2).	50mg/m^2 (d1,3,5) in course 2, with Ara-C 100mg/m^2 12-hourly d1-10 (course 1) and d1-8 (course 2).	promyelocytic leukaemia) and high-risk myelodysplastic syndrome (MDS), predominantly aged 18-60 years. Subgroup of patients with FLT3-ITD mutation was used in the analysis.		

Abbreviations: see List of abbreviations.

List of ongoing and planned studies

Table A11: List of ongoing and planned studies

Trial (NCT number)	Status	Therapy (drugs)	Phase of study	Patients	Expected date of reporting	
					Primary completion	Study completion
NCT02668653	Recruiting	Cytarabine, Daunorubicin, Idarubicin, Quizartinib	3	Newly Diagnosed FLT3-ITD (+) AML	January 2020	—
NCT00651261	Active, not recruiting	Cytarabine, Daunorubicin, Midostaurin, dexamethasone acetate	3	Newly Diagnosed AML	July 2016	—
NCT01371981	Recruiting	Asparaginase, Bortezomib, Cytarabine, Daunorubicin, Etoposide, Mitoxantrone, Sorafenib Tosylate	3	Newly Diagnosed AML	June 2017	—

ACTRN12611001112954	Not recruiting	Cytarabine, Idarubicin, Sorafenib	2	Untreated AML patients with FLT3-ITD mutation	—	—
EUdraCT no. 2008-004968-40	Completed	Sorafenib with standard primary therapy	2	Newly Diagnosed AML	—	September 2014
EUdraCT no. 2006-006852-37/ NCT00651261 (RATIFY)	Not recruiting, ongoing	Midostaurin, cytarabine, daunorubicin, SCT	3	Newly Diagnosed FLT3-ITD AML	June 2016	—
EUdraCT no. 2005-005966-35	Completed	Sorafenib with standard primary therapy	2	Newly Diagnosed AML	—	July 2009

Abbreviations: see List of abbreviations.
Source: [17]

Risk of bias tables

Table A12: Risk of bias – study level (RCTs)

Trial	Random sequence generation	Allocation concealment	Blinding of: Participants	Blinding of: Medicinal personnel	Blinding of: Outcome assessment (patient-reported outcomes, all-cause mortality)	Selective outcome reporting	Incomplete outcome data (short-term, long-term)
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low	Low	Low
UK NCRI AML17 trial	Unclear[1]	Low[2]	Unclear[3]	Unclear[3]	Unclear[3]	Low[4]	Low/unclear[5]

Comments:

1) No information was provided on random sequence generation. However, this does not mean that there would be problems in this respect.
2) Telephone randomisation.
3) The protocol or related articles does not clearly describe the nature of blinding.
4) All the relevant outcomes were reported but some of the additional outcomes (unrelated to this assessment) were not found in the publication.
5) Study was terminated early due to DMC recommendation after a signal for early mortality was seen in the daunorubicin 90 mg/m^2 arm of the trial, without any corresponding signal suggesting a later reduction in relapse. Follow-up was complete by 1st January 2014, with a median follow-up for survival of 14.8 months (range, 2.5–27.6) and results are available for this period. Furthermore, results from longer follow-up, based on subgroup of FLT3 positive patients is published [11] .

Abbreviations: see List of abbreviations.

Sources: [17], [10], [11], [56]

Table A13: Risk of bias – outcome level (RCTs)

Outcome Trial	Blinding – outcome assessors	ITT principle adequately realised	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Overall survival					
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low
UK NCRI AML17 trial-subgroup analysis[1]	Low	High[2]	Low	Low	High[3]
Overall survival censored at the time of SCT					
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low

Outcome Trial	**Blinding – outcome assessors**	**ITT principle adequately realised**	**Selective outcome reporting unlikely**	**No other aspects according to risk of bias**	**Risk of bias – outcome level**
Event-free survival [EFS]					
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low
Disease-free survival [DFS]					
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low
Complete response [CR]					
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low
Cumulative incidence of relapse [CIR]					
RATIFY (CALGB 10603/ CPKC412A2301)	Low	Low	Low	Low	Low

comments:

1) This trial is evaluated only in terms of OS based on FLT3 positive patients of which is a sub-group of the whole trial population. The results of this trial is used only in OS section in this assessment.
2) Analysis of FLT3 positive patients is based on a sub-group of the FAS ITT population. Furthermore, FLT3 status of approximately 8% of the original trial population was unknown and these patients were not included into subgroup-analysis.
3) Main reasons for this judgement relies on the fact that the results are based on updated results of the sub-group analysis after 3-year follow-up, and those from full ITT population. The analysis seems to be post hoc and background information regarding of this analysis is very limited and described not enough in detail in [11].

Abbreviations: see List of abbreviations.

Sources: [17], [10], [11], [56]

Table A14: Template for GRADE assessment

Quality assessment							**Summary of findings**					**Importance**
							Number of patients		**Effect**		**Quality**	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Intervention]**	**[comparison]**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival – comparison of midostaurin in combination with standard induction and consolidation therapy vs. standard induction and consolidation therapy												
1	RCT	Not serious	Not applicable	Not serious	Not serious	None	360	357	HR=0.77 (0.63–0.95)	Median OS was 25.6 months (18.6–42.9) for placebo and 74.7 months (31.5–not estimable) for midostaurin-based therapy.	High	Critical
Overall survival – comparison of standard induction and consolidation therapy with high-dose daunorubicin (90 mg/m^2) used in induction vs. midostaurin in combination with standard induction and consolidation therapy												
2	RCT	Serious [1]	Not applicable	Serious	Serious	Full details of the FLT3 mutated subpopulation were not available were not available for the study comparing 90 mg/m^2 and 60 mg/m^2			HR=0.84 (0.54–1.31)	—	Low/Very low	Critical/Important

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Intervention]**	**[comparison]**	**Relative (95% CI)**	**Absolute (95% CI)**		
						daunorubicin, and thus does not allow assessment of similarity of the patient groups compared indirectly. Estimate for daunorubicin 90 mg/m^2 effect is based on subgroup analysis. Follow-up time for OS differ between the UK NCRI AML17 and RATIFY trials, being only 3 years in the former.						
Overall survival censored at the time of SCT – comparison of midostaurin in combination with standard induction and consolidation therapy vs. standard induction and consolidation therapy												
1	RCT	Not serious	Not applicable	Not serious	Not serious	None	360	357	HR=0.75 (0.54–1.03)	Medians were achieved neither in midostaurin nor placebo	High	Important

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
										groups		
Event-free Survival [EFS] – comparison of midostaurin in combination with standard induction and consolidation therapy vs. standard induction and consolidation therapy												
1	RCT	Not serious	Not applicable	Not serious	Not serious	None	360	357	HR 0.73 (0.61–0.87)	Median EFS was 10.2 for midostaurin and 5.6 months for placebo arms.	High	Important
Disease-free Survival [DFS] from first complete response [CR] – comparison of midostaurin in combination with standard induction and consolidation therapy vs. standard induction and consolidation therapy												
1	RCT	Not serious	Not applicable	Not serious	Not serious	None	360	357	HR 0.66 (0.52–0.85)	Median DFS was 28.1 for midostaurin and 14.1 months for placebo arms.	High	Important
Complete response [CR; all CRs occurring during the induction] – comparison of midostaurin in combination with standard induction and consolidation therapy vs. standard induction and consolidation therapy												
1	RCT	Not serious	Not applicable	Not serious	Not serious	None	360	357	RR=1.12[2] (1.00–1.26)	Proportion of patients with CR was 65.0% for midostaurin and 58.0% months for	High	Important

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
										placebo arms. This converts to absolute risk-reduction of 7% (-0.12–14.12)[2]. The point estimate equals to NNT (number needed to treat) = 14[2].		
Cumulative Incidence of Relapse [CIR] – comparison of midostaurin in combination with standard induction and consolidation therapy vs. standard induction and consolidation therapy												
1	RCT	Not serious	Not applicable	Not serious	Not serious	None	234	207	HR=0.68 (0.52–0.89)	Median for CIR was not achieved for midostaurin. Median CIR was 17.6 months for placebo group.	High	Important
comments:												

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		

1) See table A5 and comments related to sub-group analysis of UK AML 17 trial.
2) Calculated by assessors.

Abbreviations: see List of abbreviations.

Applicability tables

Table A15: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The average age of patients in RATIFY trial was 45.2 years, which is likely to be less than the average age of those typically treated in clinical practice. It is also expected that midostaurin will be used also on patients over 60 years of age. However, patients over 60 years old have not been studied in RCT setting and there is little evidence available concerning elderly population even though age itself is not the limiting factor when using midostaurin but rather patients' fit for chemotherapy. Another feature of the patients in the RATIFY trial is the high proportion (57%) of patients receiving SCT. Also, MAH had expected lower proportion in the original sample size calculation. Possible explanation could be that the recruited patients are younger than those typically treated in clinical practice and furthermore (as typical for trials) are a selected sample of the population of interest.
Intervention	See below (comparators)
Comparators	It is likely that there is variation in the standard induction and consolidation chemotherapy across countries and regions. Midostaurin has been studied in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and with patients in complete response followed by midostaurin monotherapy. There is no evidence of midostaurin in combination with other induction and consolidation alternatives except those used in RATIFY.
Outcomes	There is evidence regarding OS for a long follow-up. Clinical benefits that support OS have also been demonstrated. Clear limitation related to applicability of the results in terms of outcomes, is the lack of HrQoL data.
Setting	No setting related applicability issues.

Abbreviations: see List of abbreviations.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Midostaurin received European market authorization via central procedure and will obtain market authorization in all European and EEA countries. Reimbursement status could not be decided in the member states at the time this assessment was written.

Daunorubicin and cytarabine are extensively used all over Europe and are reimbursed in all European/EEA countries.

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	No
Example: The marketing authorisation holder claims that its product is superior, but has decided to limit the amount of the new medicine, which means that it has to be rationed and not all patients who need it can receive it. The comparator is freely available.	
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	No
Examples: The new medicine will replace a surgical intervention which may lead to excess capacity in relevant areas. The new intervention requires the establishment of specialised centres for administration	
3. Social	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	No
Example: A medicine which is widely used by persons with abuse problems and which colours the tongue blue, thus immediately identifying the user as such. Comparators do not have this property.	
4. Legal	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	No
Examples: The comparator for the new medicine is a pharmaceutical which is not licensed in the indication of concern, but widely in use. *The comparator for the new pharmaceutical is a controlled, restricted substance, the new medicine is not.* *Note: The assessment should not address patent-related issues.*	

For the purpose of transparency, a separate document with comments on the 3rd draft assessment from external experts and the MAH/manufacturer(s) (factual accuracy check), as well as responses from authors, is available on the EUnetHTA website. Please find the link here.